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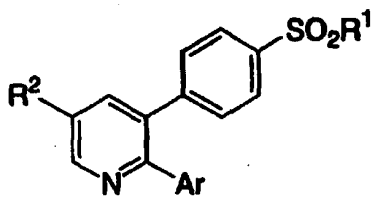
(54) Title: PROCESS FOR MAKING DIARYL PYRIDINES USEFUL AS COX-2 INHIBITORS



(I)

(57) Abstract

The invention encompasses a process for making compounds of Formula (I) useful in the treatment of cyclooxygenase–2 mediated diseases.

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INTERNATIONAL SEARCH REPORT

Int. ional Application No
PCT/US 98/19788

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D213/61 C07C223/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 24584 A (SEARLE & CO ;WEIER RICHARD M (US); LEE LEN F (US); PARTIS RICHARD) 15 August 1996 see page 50, scheme VII ---	14-18, 20-32
A	EP 0 548 559 A (AMERICAN CYANAMID CO) 30 June 1993 see pages 3-4, diagrams I, III ---	14-18, 20-32
A	R.P. THUMMEL ET AL.: JOURNAL OF ORGANIC CHEMISTRY, vol. 42, no. 16, 1977, pages 2742-2447, XP002094916 EASTON US see page 2742 ---	14-18, 20-32

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 February 1999	22/03/1999

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Int ational Application No
PCT/US 98/19788

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication.where appropriate, of the relevant passages	Relevant to claim No.
A	CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 24, no. 1, 1976, pages 85-91, XP002094917 TOKYO JP see chart 1, XI to XII	14-18, 20-32
A	DE 36 34 259 A (BASF A.G.) 21 April 1988 see claims	14-18, 20-32
A	EP 0 075 727 A (LONZA AG) 6 April 1983 see claims	14-18, 20-32
X	CHEMICAL ABSTRACTS, vol. 74, no. 17, 26 April 1971 Columbus, Ohio, US; abstract no. 87279, XP002094918 see Registry Numbers 30989-82-3, 30989-83-4, 30989-84-5, 30989-85-6, 30989-86-7 & E. BREITMAIER ET AL.: CHEM. BER., vol. 104, no. 2, 1971, pages 665-667,	33
X	CHEMICAL ABSTRACTS, vol. 91, no. 23, 3 December 1979 Columbus, Ohio, US; abstract no. 193249, XP002094919 see Registry Numbers 71637-33-7, 71637-36-0 & S. GRONOWITZ ET AL.: CHEM. SCR., vol. 13, no. 1, 1979, pages 39-45,	33
X	CHEMICAL ABSTRACTS, vol. 92, no. 21, 26 May 1980 Columbus, Ohio, US; abstract no. 180583, XP002094920 see Registry Numbers 73405-93-3, 73405-94-4 & C. SKOETSCH ET AL.: CHEM. BER., vol. 113, no. 2, 1980, pages 795-799,	33
X	CHEMICAL ABSTRACTS, vol. 96, no. 25, 21 June 1982 Columbus, Ohio, US; abstract no. 217817, XP002094921 see Registry Number 81927-49-3 & R. HANKE ET AL.: CHEM. BER., vol. 115, no. 4, 1982, pages 1657-1661,	33

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INTERNATIONAL SEARCH REPORT

Inte. .ational Application No
PCT/US 98/19788

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 99, no. 19, 7 November 1983 Columbus, Ohio, US; abstract no. 158202, XP002094922 see Registry Number 87386-45-6 & L.F. TIETZE ET AL.: TETRAHEDRON LETTERS, vol. 24, no. 34, 1983, pages 3579-3582, OXFORD GB	33
X	CHEMICAL ABSTRACTS, vol. 101, no. 13, 24 September 1984 Columbus, Ohio, US; abstract no. 109885, XP002094923 see Registry Numbers 91752-75-9, 91752-76-0 & L. KANIA ET AL.: J. MOL. STRUCT., vol. 117, no. 1-2, 1984, pages 19-31,	33
X	CHEMICAL ABSTRACTS, vol. 103, no. 13, 30 September 1985 Columbus, Ohio, US; abstract no. 104142, XP002094924 see Registrx NUmber 97988-75-5 & W. FABIAN: THEOCHEM, vol. 22, 1985, pages 287-297,	33
X	CHEMICAL ABSTRACTS, vol. 110, no. 9, 27 February 1989 Columbus, Ohio, US; abstract no. 74786, XP002094925 see Registry Number 116952-07-9 & L.F. TIETZE ET AL.: CHEM. BER., vol. 122, no. 1, 1989, pages 83-94,	33
X	CHEMICAL ABSTRACTS, vol. 115, no. 7, 19 August 1991 Columbus, Ohio, US; abstract no. 70882, XP002094926 see Registry Number 135304-92-6 & Z. ARNOLD ET AL.: COLLECT. CZECH. CHEM. COMMUN., vol. 56, no. 5, 1991, pages 1019-1031,	33

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1

INTERNATIONAL SEARCH REPORT

Int. .tional Application No
PCT/US 98/19788

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 123, no. 17, 23 October 1995 Columbus, Ohio, US; abstract no. 228067, XP002094927 see Registry Numbers 168145-51-5, 168145-52-6 & S. LINSTROEM: ACTA CHEM. SCAND., vol. 49, no. 5, 1995, pages 361-363, ---	33
X	CHEMICAL ABSTRACTS, vol. 115, no. 13, 30 September 1991 Columbus, Ohio, US; abstract no. 135894, XP002094928 see Registry Number 135987-12-1 & S KAJIGAESHI ET AL.: CHEM. EXPRESS , vol. 6, no. 7, 1991, pages 527-530, ---	33
X	US 3 277 103 A (S. TROFIMENKO) 4 October 1966 see examples 1,2 ---	33
X	EP 0 017 438 A (AMERICAN CYANAMID CO) 15 October 1980 see page 6, compounds (XV) -----	33

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INTERNATIONAL SEARCH REPORT

information on patent family members

Inter onal Application No
PCT/US 98/19788

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9624584 A	15-08-1996	US 5686470 A	11-11-1997
		AU 4859396 A	27-08-1996
		EP 0808304 A	26-11-1997
EP 0548559 A	30-06-1993	BR 9205166 A	29-06-1993
		CA 2086281 A	28-06-1993
		JP 5255259 A	05-10-1993
DE 3634259 A	21-04-1988	DE 3752066 D	19-06-1997
		EP 0263464 A	13-04-1988
		JP 1090171 A	06-04-1989
		JP 7107050 B	15-11-1995
		US 5079367 A	07-01-1992
EP 0075727 A	06-04-1983	CH 660733 A	15-06-1987
		AT 24717 T	15-01-1987
		DK 425282 A,B,	30-03-1983
		IE 54022 B	24-05-1989
		US 4421921 A	20-12-1983
US 3277103 A	04-10-1966	NONE	
EP 0017438 A	15-10-1980	US 4242515 A	30-12-1980
		AT 2674 T	15-03-1986
		AU 533295 B	17-11-1983
		AU 5519680 A	02-10-1980
		CA 1146554 A	17-05-1983
		DD 150466 A	02-09-1981
		JP 55130977 A	11-10-1980

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A1

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(30) Priority Data:
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(74) Agent: TAKASHIMA, Hajime; Yuki Building, 3–9, Hiranomachi 3–chome, Chuo–ku, Osaka–shi, Osaka 541–0046 (JP).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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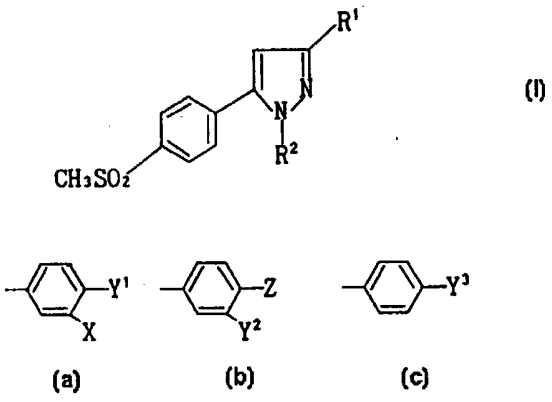
(54) Title: 1,5–DIPHENYLPYRAZOLE DERIVATIVES



(I)

(57) Abstract

A compound of formula (I), wherein R^1 is chloro, difluoromethyl, trifluoromethyl or cyano, R^2 is (a), (b), or (c), wherein X is halogen, cyano, nitro or amino, Y^1 and Y^2 are respectively lower alkyl or lower alkoxy, Y^3 is ethyl, n–propyl or isopropyl, and Z is hydrogen or halogen, processes for their preparation and pharmaceutical compositions.

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DESCRIPTION

1,5-DIPHENYLPYRAZOLE DERIVATIVES

Technical Field

This invention relates to novel pyrazole compounds and the salts thereof having pharmacological activity; to a process for their production; and to a pharmaceutical composition containing the same.

Background of Art

Some pyrazole derivatives having antiinflammatory and analgesic activities have been known as described, for example, in Canadian Patent 1 130 808, and EP Patent Publication Nos. 248 594, 272 704, 293 220, 418 845 and 554 829, and WO Patent Publication Nos. 95/15315, 95/15316, 95/15317, 95/15318, 96/14302 and 97/15271.

Disclosure of the Invention

One object of this invention is to provide the novel pyrazole compounds and salts thereof which have an inhibiting activity of cyclooxygenase-2.

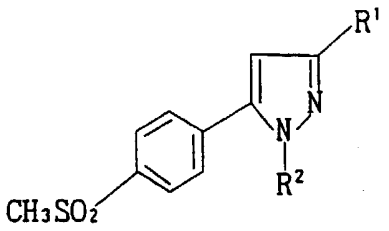
Another object of this invention is to provide the process for production of the novel pyrazole compounds.

A further object of this invention is to provide the pharmaceutical composition containing, as an active ingredient, the pyrazole compound or a salt thereof.

A still further object of this invention is to provide a use of the novel pyrazole compounds and salts thereof for manufacturing a medicament for treating or preventing various diseases.

The present invention relates to the novel pyrazole compounds and the salts thereof, which have pharmaceutical activity such as inhibiting activity of cyclooxygenase-2 (hereinafter described as COX-II), to a process for their production, to a pharmaceutical composition containing the same, and to a use thereof.

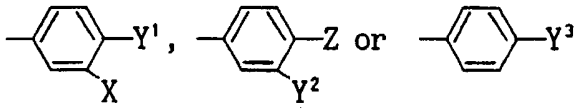
The object pyrazole derivatives of this invention are new and can be represented by the following general formula (I).



(I)

wherein R^1 is chlorine, difluoromethyl, trifluoromethyl or cyano, and

R^2 is a group having the following formula



wherein

X is halogen, cyano, nitro or amino,

Y^1 is lower alkyl or lower alkoxy,

Y^2 is lower alkyl or lower alkoxy,

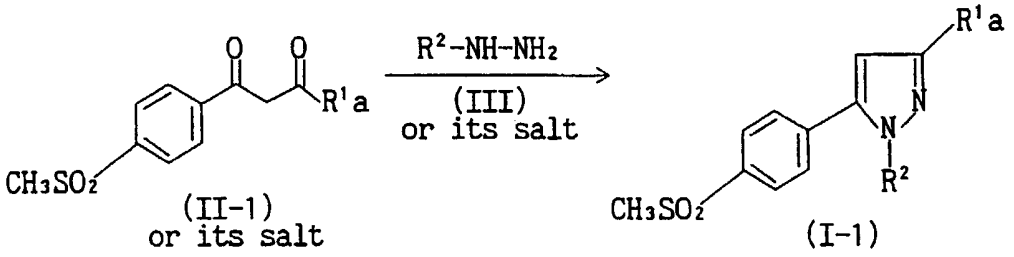
Y^3 is ethyl, n-propyl or isopropyl, and

Z is hydrogen or halogen,

and a salt thereof.

The object compound (I) can be prepared by one of the following processes 1 - 4.

Process 1

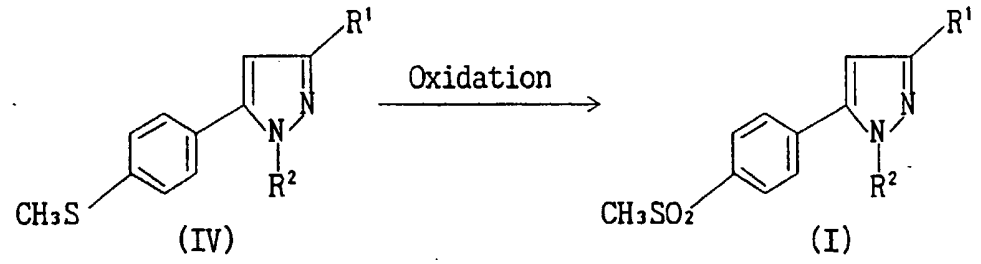


(II-1) or its salt

(III) or its salt

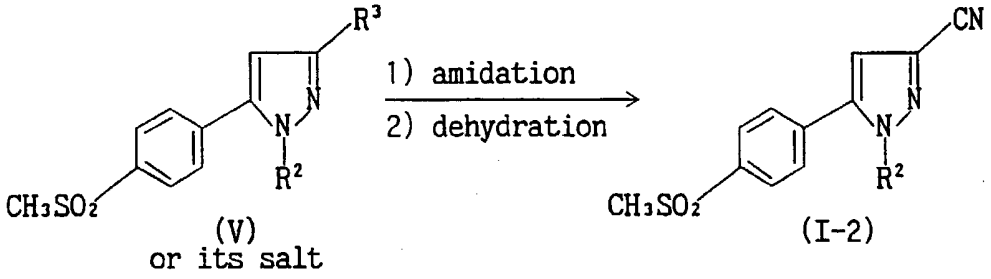
(I-1)

Process 2



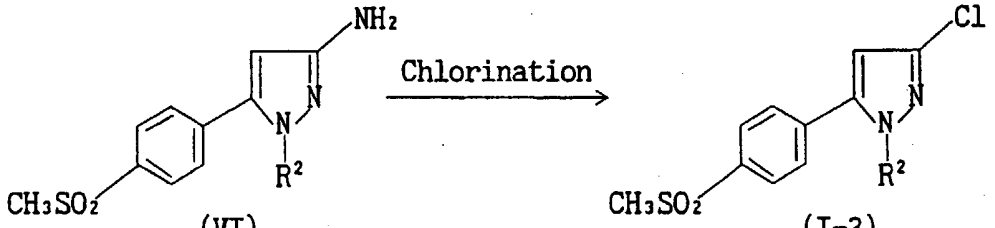
(IV) (I)

Process 3



(V) or its salt (I-2)

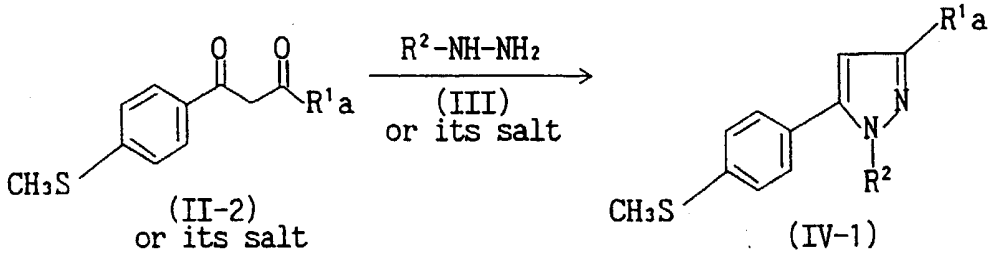
Process 4



(VI) or its salt (I-3)

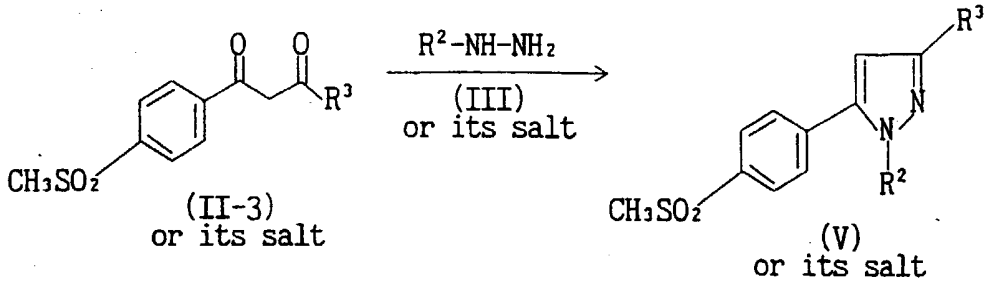
Reference Processes

(1)



(II-2) or its salt (IV-1)

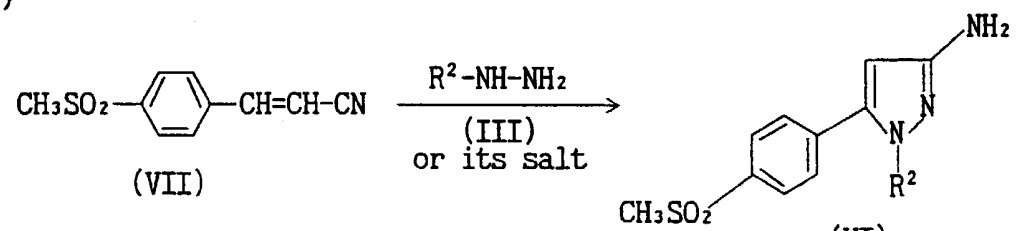
(2)



(II-3)
or its salt

(V)
or its salt

(3)



(VII)

(VI)
or its salt

wherein R^1 and R^2 are each as defined above,

R^1a is difluoromethyl or trifluoromethyl, and

R^3 is carboxy or esterified carboxy.

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having 1 to 6 carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and lower alkyl moiety in the terms "lower alkoxy" may be a straight or branched one such as methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, in which preferable one is methyl.

Suitable "lower alkoxy" may be methoxy, ethoxy, and the like, in which preferable one is methoxy.

Suitable "halogen" may be fluorine, chlorine, bromine and iodine.

Suitable "esterified carboxy" may be lower alkoxycarbonyl, such as methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, and the

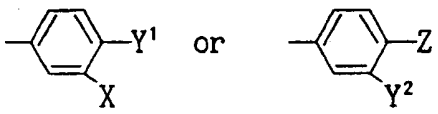
like, in which preferable one is ethoxycarbonyl.

In the compounds (I), the preferred ones are recited.

Compounds having the formula (I)

wherein R^1 is chlorine, difluoromethyl, trifluoromethyl or cyano, and

R^2 is a group having the formula



wherein X is halogen, cyano or nitro,

Y^1 is lower alkyl or lower alkoxy,

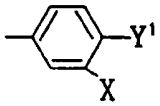
Y^2 is lower alkyl or lower alkoxy, and

Z is hydrogen or halogen.

Compounds having the formula (I)

wherein R^1 is chlorine, and

R^2 is a group having the formula

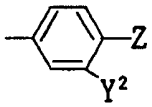


wherein X is halogen or cyano, and Y^1 is lower alkoxy.

Compounds having the formula (I)

wherein R^1 is trifluoromethyl, and

R^2 is a group having the formula

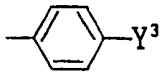


wherein Y^2 is lower alkyl, and Z is hydrogen.

Compounds having the formula (I)

wherein R^1 is chlorine or trifluoromethyl, and

R^2 is a group having the formula



wherein Y^3 is ethyl, n-propyl or isopropyl.

The more preferred one is the compound selected from the group consisting of

(1) 1-(3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole,

(2) 3-chloro-1-(3-cyano-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole,

(3) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole,

(4) 3-chloro-1-(3-chloro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole,

(5) 3-chloro-1-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole,

(6) 1-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole,

(7) 3-(difluoromethyl)-1-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole,

(8) 3-chloro-1-(4-chloro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole,

(9) 1-(4-chloro-3-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile,

(10) 3-chloro-1-(4-isopropylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole and

(11) 3-chloro-1-(3-chloro-4-ethylphenyl)-5-[4-(methylsulfonyl)-pheny]pyrazole.

The compounds (I) according to the present invention may contain one or more asymmetric centers, and thus they can exist as enantiomers or diastereoisomers, and the invention includes both mixtures and separate individual isomers.

Suitable salts of the compounds (I) are conventional pharmaceutically acceptable salts and may include a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt, cesium salt, etc.), an alkaline earth metal salt (e.g. calcium salt,

magnesium salt etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), etc.; an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.); and the like, and the preferable example thereof is an acid addition salt.

The compound (I) according to the present invention can be in the form of a solvate, which was included within the scope of the present invention. The solvate preferably includes a hydrate, an ethanolate, and so on.

Also included in the scope of invention are radiolabelled derivatives of compounds (I) which are suitable for biological studies.

Process 1

The compound (I-1) can be prepared by reacting the compound (II-1) or its salt with a hydrazine derivative (III) or its salt.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.], alkanoic acid, tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof, preferably, acidic solvent such as alkanoic acid (e.g., acetic acid).

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 2

The compound (I) can be prepared by reacting a compound (IV) with an oxidizing agent.

The suitable oxidizing agent may be hydrogen peroxide, cumene hydroperoxide, tert-butyl hydroperoxide, Jones reagent, peracid [e.g. peracetic acid, perbenzoic acid, m-chloroperbenzoic acid, monopersulfate compound (Oxone®), etc.], chromic acid, potassium permanganate, alkali metal periodate [e.g. sodium periodate, etc.], and the like.

This reaction is usually carried out in a solvent which does not adversely influence the reaction such as acetic acid, dichloromethane, acetone, ethyl acetate, chloroform, water, an alcohol [e.g. methanol, ethanol, etc.], a mixture thereof or the like.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 3

The compound (I-2) can be prepared from the compound (V) or its salt by the following methods. Namely, (i) the compound (V) or its salt can be subjected to an amidation to give a corresponding carbamoyl derivatives, and then (ii) the corresponding carbamoyl derivatives can be subjected to a dehydration to give the compound (I-2).

Amidation is carried out in a conventional manner, which is capable of converting carboxy group or protected carboxy group to carbamoyl group. Amidation can preferably carried out by, for example, (i) reacting the compound (V), wherein R^2 is esterified carboxy, with alkanoylamine (e.g., acetamide, formamide, etc.) in the presence of organic base (e.g., sodium alkoxide, etc.) or (ii) reacting the compound (V), wherein R^2 is carboxy, or its salt, with ammonia or its salt in the presence of condensing agent.

Dehydration is carried out in the conventional manner, which is capable of dehydrating a carbamoyl group to cyano group, and suitable dehydrating agent may be phosphorus compound (e.g., phosphorus oxychloride, etc.) or the like.

The reaction is usually carried out in a conventional solvent such as alcohol [e.g., methanol, ethanol, isopropyl alcohol, etc.],

tetrahydrofuran, dioxane, toluene, methylene chloride, chloroform, N,N-dimethylformamide, or any other organic solvents which do not adversely affect the reaction, or the mixture thereof.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process 4

The compound (I-3) can be prepared by the following methods.

Namely, 1) the compound (VI) or its salt is firstly reacted with a nitrite compound, and then 2) the resulting product is reacted with cuprous chloride.

Suitable nitrite compound may be alkali metal nitrite [e.g. sodium nitrite, potassium nitrite, etc.], alkyl nitrite [e.g. isoamyl nitrate, tert-butyl nitrite, etc.], and the like.

In the first step, the reaction is preferably carried out in the presence of an acid [e.g. hydrochloric acid, sulfuric acid, etc.].

The reaction is usually carried out in a solvent such as water, tetrahydrofuran, dioxane, acetonitrile, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out under cooling to warming.

In the second step, the reaction is preferably carried out in the presence of alkali metal halide [e.g. sodium chloride, etc.] and an inorganic acid [e.g. hydrochloric acid, etc.].

The reaction is usually carried out in a solvent such as water, tetrahydrofuran, dioxane, or any other organic solvent which does not adversely influence the reaction, or a mixture thereof.

The reaction temperature is not critical and the reaction can be carried out warming to heating.

Reference Processes

The compound (IV), (V) and (VI) are prepared by reacting the compound (III) with the compounds (II-2), (II-3) and (VII) respectively in a similar manner to those of Process 1 and below mentioned Preparations.

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

Suitable salts of the compounds (III) and (VI) include an organic acid addition salt [e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.], an inorganic acid addition salt [e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.], and the like.

Suitable salts of the compound (II-1), (II-2), (II-3) and (V) are an alkali metal salt [e.g. sodium salt, potassium salt, etc.], an alkaline earth metal salt [e.g. calcium salt, magnesium salt, etc.], and the like.

The object compound (I) possesses inhibiting activity of COX-II and possesses strong antiinflammatory, analgesic, antithrombotic, anti-cancer activities and so on. The object compound (I) and pharmaceutically acceptable salts thereof, therefore, are useful for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunological diseases, thrombosis, cancer and neurodegenerative diseases in human beings or animals, and more particularly for the treatment and/or prevention of inflammation and pain in joint and muscle [e.g. rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis, juvenile arthritis, etc.], inflammatory skin condition [e.g. sunburn, burns, eczema, dermatitis, etc.], inflammatory eye condition [e.g. conjunctivitis, etc.], lung disorder in which inflammation is involved [e.g. asthma, bronchitis, pigeon fancier's disease, farmer's lung, etc.], condition of the gastrointestinal tract associated with inflammation [e.g. aphthous ulcer, Chrohn's disease, atopic gastritis, gastritis varialoforme, ulcerative colitis, coeliac disease, regional ileitis, irritable bowel syndrome, etc.], gingivitis, inflammation, pain and tumescence after operation or injury, pyrexia, pain and other conditions associated with

inflammation, particularly those in which lipoxygenase and cyclooxygenase products are a factor, systemic lupus erythematosus, scleroderma, polymyositis, tendinitis, bursitis, periarteritis nodosa, rheumatic fever, Sjogren's syndrome, Behcet disease, thyroiditis, type I diabetes, nephrotic syndrome, aplastic anemia, myasthenia gravis, uveitis contact dermatitis, psoriasis, Kawasaki disease, sarcoidosis, Hodgkin's disease, Alzheimer's disease, and the like. Additionally, the object compound (I) or a salt thereof is expected to be useful as therapeutical and/or preventive agents for cardiovascular or cerebrovascular diseases, the diseases caused by hyperglycemia and hyperlipemia.

The compound (I) of the present invention has much advantage, such as more selective inhibitory activity of COX-II, stronger activity, more suitable half-life, decreased adverse effect, or the like, compared to the known pyrazole compounds shown in the prior arts.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the compound (I) are shown in the following.

[A] ANTIINFLAMMATORY ACTIVITY :

Effect on adjuvant arthritis in rats :

(i) Test Method :

Ten female Sprague-Dawley rats were used per group. A dose of 0.5 mg of Mycobacterium tuberculosis (strain M37 BA) suspended in 0.05 ml of liquid paraffin was injected subcutaneously in the right hind paw. The injection of mycobacterial adjuvant produced local inflammatory lesions (primary lesion) and then about 10 days later, secondary lesions in both the injected and uninjected paws. The volumes of both paws before and on days 23 after the injection was measured as percent inhibition in comparison to vehicle-treated controls. The drug was given orally once a day for 23 consecutive days from day 1 after the injection.

(ii) Test Results :

[A] ANTIINFLAMMATORY ACTIVITY

Test compound (Example No.)	Dose (mg/kg)	Inhibition of secondary lesion (uninjected paw) (%)
1	1.0	≧60
10-(8)	1.0	≧60

[B] COX-I and COX-II activity in vitro :

(i) Test Method :

a. Preparation of the recombinant cyclooxygenase (COX)

The human cyclooxygenase COX-I and COX-II were expressed in transfected Chinese hamster ovary (CHO) cells. Monolayer cultures of semi-confluent CHO cells stably expressing COX-I and COX-II were washed twice and scraped into phosphate buffered saline (PBS). The cells were centrifuged at 200 x g for 5 minutes and the cell pellet was sonicated in reaction buffer containing 100 mM Tris-HCl (pH 7.4), 2 μM hematin and 5 mM tryptophan. Broken cells were centrifuged for 5 minutes at 1700 x g at 4℃ and the supernatants were used as crude enzymes.

Cyclooxygenase activities in the absence or presence of inhibitors were measured by determining the level of prostaglandin E_2 (PGE_2) synthesis from arachidonic acid. Enzymes (1 μg for COX-I and/or 3 μg for COX-II) in a total volume of 200 μl of reaction buffer were incubated in the absence and presence of various concentrations of inhibitors for 5 minutes at 30 ℃. The reaction was then started by the addition of arachidonic acid to the final concentration of 10 μM. The reaction was terminated by 50 μl of HCl (1N) after incubation at 30℃ for 5 minutes. PGE_2 was extracted with ethyl acetate, concentrated under a stream of nitrogen and analyzed by a radio immunoassay kit (Amersham) according to the manufacture's instructions.

b. Assay for human recombinant COX-I and COX-II activity

COX activity was assayed as PGE_2 formation using radioimmunoassay to detect the prostaglandin release. The appropriate COX enzyme was

incubated in 0.1 M Tris-HCl buffer (pH 7.3) containing hematin and tryptophan with the addition of arachidonic acid (10 μM) for 5 minutes at 37℃. Compounds were pre-incubated with the enzyme for 5 minutes prior to the addition of arachidonic acid. Any reaction between the arachidonic acid and the enzyme was stopped after 5 minutes at 37℃ by addition of 20μl of 1N HCl. PGE_2 formation was measured by radioimmunoassay (Amersham).

(ii) Test Results :

[B] COX-I and COX-II activitv in vitro :

Test compound (Example No.)	Human COX-II IC_{50} (μM)	Human COX-I IC_{50} (μM)
3-(16)	<1	>100
6	<1	>100
10-(8)	<1	>100

The compound (I) and a pharmaceutically acceptable salt thereof, are used as a medicament by intravenous, intracutaneous, intramuscular, pulmonary, or oral administration, or insufflation to human beings or animals.

A pharmaceutical composition of the present invention is a homogeneous mixture which comprises one of the compounds (I) or pharmaceutically acceptable salts thereof, as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient. The pharmaceutical composition is manufactured by mixing the sufficient amount of the compound (I) or a salt thereof as an active ingredient with a pharmaceutically non-toxic carrier or excipient to give homogeneous mixture. The pharmaceutically non-toxic carriers and excipients may be organic or inorganic and solid or liquid, and can be any of the conventional ones suitable for oral, parenteral or external (topical) administration.

For therapeutic purpose, the pharmaceutical composition of the present invention can be used in a form of a pharmaceutical preparation, for example, in a solid, semisolid, or liquid form. The pharmaceutical preparations may be capsules, tablets, dragees,

granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

In the pharmaceutical composition the compound (I) or a pharmaceutically acceptable salt thereof is included in an sufficient amount to have the desired effects of aforementioned pharmaceutical activities on the aforesaid diseases in human beings or animals.

While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of the patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

The patents, patent applications and publications cited herein are incorporated by reference.

The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

To acetic anhydride (20 ml) was added 70% nitric acid (2 ml) dropwise in an ice-bath. During the addition, the internal temperature of the mixture temporarily rose to 25 ℃ and dropped to 0℃. To the mixture was added 1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (2.0 g) portionwise. The reaction mixture was allowed to stir for 5 hours and poured into ice-water. The precipitate formed was collected by filtration and dried to give 1-(4-methoxy-3-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (2.15 g).

An analytical sample was prepared by recrystallization from ethanol.

mp : 175-177℃ (ethanol)

IR (KBr) : 1540, 1361, 1313, 1160, 1141 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.96 (3H, s), 7.39 (1H, s), 7.44 (1H, d, J=8Hz), 7.5-7.7 (2H, m), 7.65 (1H, dd, J=2, 8Hz), 7.9-8.0 (2H, m), 8.09 (1H, d, J=2Hz)

MASS : 442 $(M+H)^+$

Preparation 2

A mixture of 1-(4-methoxy-3-nitrophenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trifluoromethyl)pyrazole (2.15 g), activated carbon (2.15 g), anhydrous iron(III) chloride (100 mg), hydrazine monohydrate (2.2 ml), ethanol (75 ml), and tetrahydrofuran (75 ml) was refluxed for 3.5 hours. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography on silica gel (gradient elution; 10:1 chloroform-ethyl acetate to 100:10:1 chloroform-ethyl acetate-methanol) to give the product, which was dissolved in ethyl acetate (10 ml) and treated with a solution of 4N hydrogen chloride in ethyl acetate (5 ml). The resultant solid was collected by filtration to give 1-(3-amino-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-pyrazole hydrochloride (1.92 g).

mp : 214-220℃ (ethanol)

IR (KBr) : 3424, 2003, 1631, 1313, 1160, 1157, 1132 cm^{-1}

NMR (DMSO-d_6, δ) : 3.26 (3H, s), 3.87 (3H, s), 5.0-7.0 (3H, br m), 6.98 (1H, dd, J=2, 8Hz), 7.09 (1H, d, J=8Hz), 7.23 (1H, d, J=2Hz), 7.34 (1H, s), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

MASS : 412 $(M+H)^+$

Preparation 3

A solution of sodium nitrite (6 g) in water (50 ml) was added dropwise to a solution of 3-chloro-4-methoxyaniline (10 g) in concentrated hydrochloric acid (30 ml) at 0℃ with stirring. After the addition was completed, the reaction mixture was stirred at the

same temperature for 1 hour. A solution of stannous chloride dihydrate (50 g) in concentrated hydrochloric acid (30 ml) was added dropwise at 0℃. The resulting mixture was stirred for 2 hours at the same temperature. The resulting precipitate was collected by filtration, washed with ice water and dried in vacuo at 50℃ to afford (3-chloro-4-methoxyphenyl)hydrazine hydrochloride (11.5 g) as a yellow brown solid.

mp : 240-250℃ (decomp.)

IR (Nujol) : 3200, 2700, 1600, 1570, 1505, 1290 cm^{-1}

NMR (DMSO-d_6, δ) : 3.80 (3H, s), 6.98 (1H, dd, J=2.7, 8.9Hz), 7.09-7.17 (2H, m) , 8.12 (1H, br s), 10.14 (3H, br s)

MASS : 173 $(M+H)^+$

Preparation 4

The mixture containing 4,4-difluoro-1-[(4-methylthio)phenyl]-butane-1,3-dione (1.0 g), (3-chloro-4-methoxyphenyl)hydrazine hydrochloride (0.94 g) and acetic acid (20 ml) was stirred at 100-110℃. After 2 hours, the reaction mixture was concentrated in vacuo. The resultant residue was partitioned between ethyl acetate and water. The organic layer was separated, washed with water and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure gave 1-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)-5-[4-(methylthio)phenyl]pyrazole (2.10 g) as an oil.

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 3.91 (3H, s), 6.75-7.26 (2H, m), 6.69 (1H, s), 7.13 (2H, d, J=8.0Hz), 7.18 (2H, d, J=8.0Hz), 7.45 (1H, d, J=2.5Hz)

MASS : 381 $(M+H)^+$

Preparation 5

The following compounds described in (1) to (11) were obtained according to a similar manner to that of Example 2.

(1) Ethyl 1-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carboxylate

IR (KBr) : 3008, 1712, 1309, 1224, 1153 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.1Hz), 2.28 (3H, d, J=1.6Hz),

3.07 (3H, s), 4.47 (2H, q, J=7.1Hz), 6.95-7.00 (2H, m), 7.13 (1H, s), 7.31 (1H, d, J=7.0Hz), 7.42 (2H, d, J=8.6Hz), 7.90 (2H, d, J=8.6Hz)

MASS : 403 $(M+H)^+$

(2) Ethyl 1-(4-chloro-3-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carboxylate

IR (KBr) : 3127, 3000, 1710, 1313, 1234, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.1Hz), 2.38 (3H, s), 3.08 (3H, s), 4.47 (2H, q, J=7.1Hz), 6.93 (1H, dd, J=8.4, 2.3Hz), 7.30 (1H, d, J=8.4Hz), 7.37 (1H, d, J=2.3Hz), 7.43 (2H, d, J=8.6Hz), 7.92 (2H, d, J=8.6Hz)

MASS : 419 $(M+H)^+$ (^{35}Cl), 421 $(M+H)^+$ (^{37}Cl)

(3) Ethyl 1-(4-bromo-3-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carboxylate

IR (KBr) : 3126, 3004, 1710, 1315, 1234, 1153 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.1Hz), 2.40 (3H, s), 3.08 (3H, s), 4.47 (2H, q, J=7.1Hz), 6.84 (1H, dd, J=8.4, 2.6Hz), 7.13 (1H, s), 7.37-7.47 (3H, m), 7.49 (1H, d, J=8.4Hz), 7.92 (2H, d, J=8.5Hz)

MASS : 463 $(M+H)^+$ (^{79}Br), 465 $(M+H)^+$ (^{81}Br)

(4) Ethyl 1-(4-fluoro-3-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylate

IR (KBr) : 3004, 2923, 1714, 1313, 1263, 1224, 1155 cm^{-1}

NMR ($CDCl_3$, δ) : 1.44 (3H, t, J=7.1Hz), 3.08 (3H, s), 3.85 (3H, s), 4.47 (2H, q, J=7.1Hz), 6.71 (1H, m), 6.98-7.14 (3H, m), 7.43 (2H, d, J=8.5Hz), 7.92 (2H, d, J=8.5Hz)

MASS : 419 $(M+H)^+$

(5) Ethyl 1-(4-chloro-3-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylate

IR (KBr) : 2981, 1722, 1311, 1251, 1220, 1153 cm^{-1}

NMR ($CDCl_3$, δ) : 1.44 (3H, t, J=7.1Hz), 3.08 (3H, s), 3.85 (3H, s), 4.47 (2H, q, J=7.1Hz), 6.68 (1H, dd,

J=8.4, 2.3Hz), 7.05 (1H, d, J=2.3Hz), 7.14 (1H, s), 7.31 (1H, d, J=8.4Hz), 7.44 (2H, d, J=8.6Hz), 7.92 (2H, d, J=8.6Hz)

(6) Ethyl 1-(4-bromo-3-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carboxylate

IR (KBr) : 2979, 1724, 1311, 1251, 1220, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 1.44 (3H, t, J=7.1Hz), 3.08 (3H, s), 3.84 (3H, s), 4.47 (2H, q, J=7.1Hz), 6.62 (1H, dd, J=8.4, 2.2Hz), 7.01 (1H, s), 7.08-7.51 (4H, m), 7.92 (2H, d, J=8.2Hz)

MASS : 479 $(M+H)^+$ (^{79}Br), 481 $(M+H)^+$ (^{81}Br)

(7) Ethyl 1-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carboxylate

IR (KBr) : 3002, 1714, 1313, 1276, 1241, 1189, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.1Hz), 2.31 (3H, d, J=1.8Hz), 3.08 (3H, s), 4.46 (2H, q, J=7.1Hz), 6.93 (1H, dd, J=8.3, 2.0Hz), 7.08 (1H, dd, J=9.5, 2.0Hz), 7.13 (1H, s), 7.20 (1H, d, J=8.3Hz), 7.42 (2H, d, J=8.5Hz), 7.91 (2H, d, J=8.5Hz)

MASS : 403 $(M+H)^+$

(8) Ethyl 1-(3-chloro-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carboxylate

IR (KBr) : 3000, 1712, 1313, 1232, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.1Hz), 2.41 (3H, s), 3.08 (3H, s), 4.47 (2H, q, J=7.1Hz), 6.98 (1H, dd, J=8.1, 2.2Hz), 7.13 (1H, s), 7.20 (1H, d, J=8.1Hz), 7.43 (2H, d, J=8.6Hz), 7.47 (1H, d, J=2.2Hz), 7.92 (2H, d, J=8.6Hz)

MASS : 419 $(M+H)^+$ (^{35}Cl), 421 $(M+H)^+$ (^{37}Cl)

(9) Ethyl 1-(3-bromo-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carboxylate

IR (KBr) : 2983, 1718, 1311, 1232, 1153 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.1Hz), 2.43 (3H, s),

3.08 (3H, s), 4.47 (2H, q, J=7.1Hz), 7.01 (1H, dd, J=8.1, 2.2Hz), 7.12 (1H, s), 7.20 (1H, d, J=8.1Hz) 7.43 (2H, d, J=8.6Hz), 7.66 (1H, d, J=2.2Hz), 7.92 (2H, d, J=8.6Hz)

MASS : 463 $(M+H)^+$ (^{79}Br), 465 $(M+H)^+$ (^{81}Br)

(10) Ethyl 1-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylate

IR (KBr) : 3012, 2987, 1700, 1311, 1278, 1230, 1147 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.1Hz), 3.08 (3H, s), 3.92 (3H, s), 4.47 (2H, q, J=7.1Hz) , 6.89 (1H, d, J=8.9Hz), 6.99 (1H, dd, J=8.9, 2.3Hz), 7.11-7.26 (2H, m), 7.43 (2H, d, J=8.5Hz), 7.91 (2H, d, J=8.5Hz)

MASS : 419 $(M+H)^+$

(11) Ethyl 1-(3-chloro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylate

IR (KBr) : 2979, 1718, 1313, 1272, 1226, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (3H, t, J=7.1Hz), 3.08 (3H, s), 3.93 (3H, s), 4.47 (2H, q, J=7.1Hz), 6.87 (1H, d, J=8.8Hz), 7.06 (1H, dd, J=8.8, 2.6Hz), 7.12 (1H, s), 7.43 (2H, d, J=8.5Hz), 7.50 (1H, d, J=2.6Hz), 7.91 (2H, d, J=8.5Hz)

MASS : 435 $(M+H)^+$ (^{35}Cl), 437 $(M+H)^+$ (^{37}Cl)

Preparation 6

The following compound was obtained according to a similar manner to that of Preparation 1.

1-(4-Methoxy-3-nitrophenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

IR (KBr) : 3072, 3021, 2242, 1535, 1363, 1311, 1282, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 3.10 (3H, s), 4.02 (3H, s), 6.98 (1H, s), 7.12 (1H, d, J=9.1Hz), 7.41-7.48 (3H, m), 7.81 (1H, d, J=2.7Hz), 7.99 (2H, d, J=8.5Hz)

MASS : 399 $(M+H)^+$

Preparation 7

A mixture of 1-(4-methoxy-3-nitrophenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile (1.8 g) and ammonium chloride(0.18 g) in ethanol-water (50 ml) was stirred under 90℃. After several minutes, iron (powder) (1.8 g) was added and the resulting mixture was stirred for 1.5 hours at same temperature. After cooling, the insoluble material was filtrated off and washed with tetrahydrofuran. The filtrate was concentrated under reduced pressure to give a material which on treatment with 4N hydrogen chloride in ethyl acetate afforded 1-(3-amino-4-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile hydrochloride (1.8 g).

IR (KBr) : 3400, 2842, 2244, 1303, 1282, 1147 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.86 (3H, s), 6.86 (1H, dd, J=8.6, 2.0Hz), 7.03 (1H, d, J=8.6Hz), 7.05 (1H, d, J=2.0Hz), 7.55 (2H, d, J=8.4Hz), 7.94 (2H, d, J=8.4Hz)

MASS : 369 $(M+H)^+$

Preparation 8

To a mixture of (3-methoxyphenyl)hydrazine (6 g) and 3-[4-(methylthio)phenyl]acrylonitrile (5.7 g) in methanol (100 ml) was added sodium methoxide (28 wt. % solution in methanol) (18 ml) at ambient temperature. The mixture was heated to dryness under nitrogen at 140℃ for 30 minutes. The resultant orange mass was partitioned between dichloromethane and ice water. The organic layer was dried over magnesium sulfate, and then filtered. This filtrate was evaporated in vacuo. The resultant mass was dissolved in ethyl acetate (150 ml) and refluxed for 1 hour in the presence of magnesium(IV) oxide (20 g). This mixture was cooled, and filtered. The filtrate was evaporated in vacuo. The resultant mass was purified by column chromatography on silica gel using dichloromethane as eluent to give {1-(3-methoxyphenyl)-5-[4-(methylthio)-phenyl]pyrazol-3-yl}amine (5.2 g).

IR (Nujol) : 3450, 3320, 3220, 1630, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 3.66 (3H, s), 4.98 (2H, s), 5.81 (1H, s), 6.61-6.79 (3H, m), 7.12-7.25 (4H, m)

MASS : 312 $(M+H)^+$

Preparation 9

The following compounds described in (1) to (11) were obtained according to a similar manner to that of Preparation 8.

(1) {1-(4-Fluoro-3-methylphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

NMR (DMSO-d_6, δ) : 2.18 and 2.19 (total 3H, s), 2.45 (3H, s), 4.92 (2H, s), 5.81 (1H, s), 6.80-6.88 (1H, s), 7.02-7.23 (6H, m)

IR (KBr) : 3303, 3205, 1625, 1563, 1508 cm^{-1}

MASS : 300 $(M+H)^+$

(2) {1-(4-Chloro-3-methylphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

IR (Nujol) : 1630, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.27 (3H, s), 2.47 (3H, s), 5.00 (2H, s), 5.83 (1H, s), 6.70-6.85 (1H, m) , 7.11-7.39 (6H, m)

MASS : 330 $(M+H)^+$

(3) {1-(4-Bromo-3-methylphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

IR (Nujol) : 3450, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.29 (3H, s), 2.47 (3H, s), 5.00 (2H, s), 5.83 (1H, s), 6.71-6.77 (1H, m), 7.14 (2H, d, J=8.5Hz), 7.23 (2H, d, J=8.5Hz), 7.29 (1H, d, J=1.6Hz) , 7.46 (1H, d, J=8.6Hz)

MASS : 375 $(M+H)^+$

(4) {1-(4-Chloro-3-methoxyphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

IR (Nujol) : 3450, 3300, 3200, 1630, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 3.70 (3H, s), 5.06

(2H, s), 5.83 (1H, s), 6.59 (1H, dd, J=8.5, 2.3Hz), 6.98 (1H, d, J=2.3Hz), 7.16 (2H, d, J=8.6Hz), 7.26 (2H, d, J=8.6Hz), 7.31 (2H, d, J=8.5Hz)

MASS : 346 $(M+H)^+$

(5) {1-(3-Fluoro-4-methylphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

IR (KBr) : 3295, 3195, 1625, 1513 cm^{-1}

NMR (DMSO-d_6, δ) : 2.19 (3H, s), 2.47 (3H, s), 5.02 (2H, s), 5.82 (1H, s), 6.80 (1H, dd, J=8.1, 1.9Hz), 6.96 (1H, dd, J=11.1, 1.9Hz), 7.12-7.25 (5H, m)

MASS : 314 $(M+H)^+$

(6) {1-(3-Chloro-4-methylphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

IR (Nujol) : 3450, 3400, 3200, 1630, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 2.29 (3H, s), 2.47 (3H, s), 5.03 (2H, s), 5.82 (1H, s), 6.89 (1H, dd, J=8.2, 2.1Hz), 7.13-7.27 (6H, m)

MASS : 330 $(M+H)^+$

(7) {1-(3-Bromo-4-methylphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

This compound was used in the next reaction without purification.

(8) {1-(3-Chloro-4-methoxyphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

IR (Nujol) : 3450, 3300, 3200, 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 2.47 (3H, s), 2.50 (3H, s), 4.95 (2H, s), 5.80 (1H, s), 6.96-7.28 (7H, m)

MASS : 346 $(M+H)^+$

(9) {1-(4-Ethylphenyl)-5-[4-(methylthio)phenyl]pyrazol-3-yl}amine crystals

mp : 128-132℃

IR (Nujol) : 3490, 3460, 1620, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.13-1.23 (3H, m), 2.54 (3H, s),

2.52-2.64 (2H, m), 4.91 (2H, br s), 5.79 (1H, s),
7.03-7.56 (8H, m)

MASS : 309 $(M+H)^+$

(10) {5-[4-(Methylthio)phenyl]-1-(4-n-propylphenyl)-pyrazol-3-yl}amine

crystals

mp : 140-142℃

IR (KBr) : 3450, 3303, 3193, 1630, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=7Hz), 1.51-1.63 (2H, m), 2.46 (3H, s), 2.49-2.52 (2H, m), 4.92 (2H, br s), 5.79 (1H, s), 7.01-7.22 (8H, m)

MASS : 324 $(M+H)^+$

(11) {1-(4-Isopropylphenyl)-5-[4-(methylthio)phenyl]-pyrazol-3-yl}amine

crystals

mp : 148-150℃

IR (KBr) : 3450, 3305, 3197, 1631, 1513 cm^{-1}

NMR (DMSO-d_6, δ) : 1.18 (6H, d, J=7Hz), 2.46 (3H, s), 2.83-2.91 (1H, m), 4.92 (2H, br s), 5.79 (1H, s), 7.01-7.22 (8H, m)

MASS : 324 $(M+H)^+$

Preparation 10

The following compounds described in (1) to (2) were obtained according to a similar manner to that of Preparation 3.

(1) (4-Fluoro-3-methylphenyl)hydrazine hydrochloride

IR (KBr) : 3002, 1585, 1550 cm^{-1}

NMR (DMSO-d_6, δ) : 2.18 (3H, s), 6.8-7.15 (3H, m)

(2) (3-Fluoro-4-methylphenyl)hydrazine hydrochloride

IR (KBr) : 2994, 1631, 1585, 1515 cm^{-1}

NMR (DMSO-d_6, δ) : 2.13 (3H, s), 6.70-6.86 (2H, m), 7.16 (1H, t, J=8.5Hz)

Preparation 11

To a solution of 3-chloro-1-(3-methoxyphenyl)-5-[4-

(methylsulfonyl)phenyl]pyrazole (575 mg) in acetic anhydride (10 ml) and acetic acid (1 ml) was added nitric acid (fuming) (500 ml) at 0 ℃. After being stirred at 0℃ for 2 hours, the reaction mixture was poured into water, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and filtered. The filtrate was evaporated in vacuo, and purified by column chromatography using dichloromethane as eluent to give 3-chloro-1-(3-methoxy-4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (590 mg).

mp : 170-175℃

IR (Nujol) : 1615, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 3.26 (3H, s), 3.80 (3H, s), 6.95 (1H, dd, J=8.7, 2.1Hz), 7.34 (1H, d, J=2.0Hz), 7.60 (2H, d, J=8.4Hz), 7.95 (2H, d, J=8.6Hz), 7.97 (2H, d, J=8.4Hz)

MASS : 408 $(M+H)^+$

Preparation 12

To a solution of 3-chloro-1-(3-methoxy-4-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (900 mg) in ethanol (30 ml) and tetrahydrofuran (30 ml) were added active carbon (3 g), hydrazine monohydrate (2 ml) and ferric chloride (50 mg). The mixture was refluxed for 2 hours, and filtered. The filtrate was evaporated in vacuo and partitioned between water and dichloromethane. The organic layer was dried over magnesium sulfate and filtered. The filtrate was evaporated in vacuo to give 1-(4-amino-3-methoxyphenyl)-3-chloro-5-[4-(methylsulfonyl)phenyl]pyrazole (820 mg).

IR (Nujol) : 3350, 1630, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.23 (3H, s), 3.83 (3H, s), 5.08 (2H, s), 6.56 (2H, s), 6.81 (1H, s), 6.90 (1H, s), 7.51 (2H, d, J=8.3Hz), 7.90 (2H, d, J=8.3Hz)

MASS : 378 $(M+H)^+$

Preparation 13

A mixture of 2-methoxy-5-nitrobenzonitrile (14 g), ammonium chloride (5 g), the powder of reduced iron (9 g) in methanol was

refluxed for 4 hours and cooled. The reaction mixture was filtered and the filtrate was poured into water. The resultant precipitates were filtered and washed with water to give 3-cyano-4-methoxyaniline (7.7 g).

IR (KBr) : 3420, 3320, 2220 cm^{-1}

NMR (DMSO-d_6, δ) : 3.76 (3H, s), 5.05 (2H, br s), 6.79 (1H, d, J=2.7Hz), 6.86 (1H, dd, J=8.9, 2.7Hz), 6.96 (1H, d, J=8.9Hz)

MASS : 149 $(M+H)^+$

Preparation 14

A solution of sodium nitrite (4.0 g) in water (7 ml) was added to an ice cooled mixture of 3-cyano-4-methoxyaniline (7.7 g) and concentrated hydrochloric acid (21 ml). The mixture was stirred at 0 ℃ for 30 minutes. To the resultant mixture a solution of tin(II) chloride dihydrate (49 g) and concentrated hydrochloric acid (5 ml) was added at 0℃ and stirred for 1 hour. The precipitates were filtered and washed with ice cooled concentrated hydrochloric acid (10 ml) to give crude (3-cyano-4-methoxyphenyl)hydrazine hydrochloride (14.8 g).

NMR (DMSO-d_6, δ) : 3.87 (3H, s), 7.24 (1H, d, J=10.0Hz), 7.30-7.37 (2H, comp. m), 8.27 (1H, br s), 10.15 (3H, br s)

Preparation 15

A stirred mixture of (3-cyano-4-methoxyphenyl)hydrazine hydrochloride (3.7 g), 3-[4-(methylthio)phenyl]acrylonitrile (2.3 g) and sodium methoxide (0.9 g) in methanol 13 ml was gradually heated to 140℃ under atmospheric pressure and N_2 atmosphere, and continued to heat for 8 hours at 140℃. Ethyl acetate and water were added to the reaction mixture. The organic layer was separated, washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give crude 1-(3-cyano-4-methoxyphenyl)-5-[4-(methylthio)-phenyl]-2-pyrazoline-3-amine (4.0 g).

Preparation 16

A mixture of 1-(3-cyano-4-methoxyphenyl)-5-[4-(methylthio)phenyl]-2-pyrazoline-3-amine (4.0 g) and manganese(IV) oxide (6.0 g) in

toluene (100 ml) was stirred at ambient temperature for 8 hours. The insoluble material was filtered and washed with ethyl acetate. The resulting solution was concentrated under reduced pressure. The residue was subjected to column chromatography on silica gel eluting with a mixture of acetone and dichloromethane (1:1) to give partially purified 1-(3-cyano-4-methoxyphenyl)-5-[4-(methylthio)phenyl]-pyrazole-3-amine (1.1 g).

IR (KBr) : 2225 cm^{-1}

Preparation 17

A solution of sodium nitrite (0.36 g) in water (0.5 ml) was added to an ice cooled mixture of 1-(3-cyano-4-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazol-3-amine (1.08 g), concentrated hydrochloric acid (15 ml) and acetic acid (35 ml). The mixture was stirred at 0℃ for 30 minutes and added portionwise to a mixture of cuprous chloride (1.37 g) and concentrated hydrochloric acid (10 ml) at ambient temperature. The mixture was refluxed for 1 hour, poured into water and extracted with toluene. The extract was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel eluting with toluene to give 3-chloro-1-(3-cyano-4-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazole (0.29 g).

IR (Film) : 2230, 1600, 1500 cm^{-1}

NMR ($CDCl_3$, δ) : 2.49 (3H, s), 3.95 (3H, s), 6.41 (1H, s), 6.92 (1H, d, J=9.0Hz), 7.09 (2H, d, J=8.6Hz), 7.19 (2H, d, J=8.6Hz), 7.42 (1H, dd, J=9.0, 2.7Hz), 7.54 (1H, d, J=2.7Hz)

MASS : 356 $(M+H)^+$

Preparation 18

The following compounds described in (1) to (3) were obtained according to a similar manner to that of Preparation 11.

(1) 3-Chloro-1-(4-ethyl-3-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole

crystals

mp : 134-135℃

IR (KBr) : 1577 cm^{-1}

NMR (DMSO-d_6, δ) : 1.21 (3H, t, J=7Hz), 2.84 (2H, q, J=7Hz), 3.25 (3H, s), 7.02 (1H, s), 7.48-7.61 (4H, m), 7.89-7.94 (3H, m)

MASS : 406 $(M+H)^+$ (^{35}Cl), 408 $(M+H)^+$ (^{37}Cl)

(2) 3-Chloro-5-[4-(methylsulfonyl)phenyl]-1-(3-nitro-4-n-propylphenyl)pyrazole

crystals

mp : 42-46℃

IR (KBr) : 1535 cm^{-1}

NMR (DMSO-d_6, δ) : 0.91 (3H, t, J=7Hz), 1.54-1.65 (2H, m), 2.79 (2H, t, J=7Hz), 3.25 (3H, s), 7.07 (1H, s), 7.46-7.61 (4H, m), 8.27-8.32 (3H, m)

MASS : 420 $(M+H)^+$

(3) 1-(4-Isopropyl-3-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

crystals

mp : 64-69℃

IR (KBr) : 1536 cm^{-1}

NMR (DMSO-d_6, δ) : 1.25 (6H, d, J=7Hz), 3.20 (1H, m), 3.27 (3H, s), 7.42 (1H, s), 7.76-7.59 (4H, m), 7.89 (2H, d, J=9Hz), 7.97 (1H, s)

MASS : 454 $(M+H)^+$

Preparation 19

The following compounds described in (1) to (3) were obtained according to a similar manner to that of Preparation 12.

(1) 1-(3-Amino-4-ethylphenyl)-3-chloro-5-[4-(methylsulfonyl)phenyl]-pyrazole

crystals

mp : 158-160℃

IR (KBr) : 3462, 3442, 3351 cm^{-1}

NMR (DMSO-d_6, δ) : 1.30 (3H, t, J=7Hz), 2.43 (2H, q, J=7Hz),

3.24 (3H, s), 5.19 (2H, br s), 6.30 (1H, dd, J=8, 2Hz),
6.62 (1H, d, J=2Hz), 6.8-6.9 (2H, m),
7.52 (2H, d, J=8Hz), 7.91 (2H, d, J=8Hz)

MASS : 376 $(M+H)^+$

(2) 1-(3-Amino-4-n-propylphenyl)-3-chloro-5-[4-(methylsulfonyl)-phenyl]pyrazole

crystals

mp : 152-154℃

IR (KBr) : 3461, 3350, 1628, 1595 cm^{-1}

NMR (DMSO-d_6, δ) : 0.92 (3H, t, J=7Hz), 1.48-1.59 (2H, m),
2.41 (2H, t, J=7Hz), 3.60 (3H, s), 5.19 (2H, br s),
6.27 (1H, dd, J=8, 2Hz), 6.61 (1H, d, J=2Hz),
6.12-6.57 (2H, m), 7.51 (2H, d, J=8Hz),
7.90 (2H, d, J=8Hz)

MASS : 390 $(M+H)^+$

(3) 1-(3-Amino-4-isopropylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

crystals

mp : 134-135℃

IR (KBr) : 3430, 3359, 1635, 1506 cm^{-1}

NMR (DMSO-d_6, δ) : 1.14 (6H, d, J=7Hz), 2.97 (1H, m),
3.26 (3H, s), 5.29 (1H, br s), 6.37 (1H, dd, J=8, 2Hz),
6.69 (1H, d, J=2Hz), 7.03 (1H, d, J=8Hz), 7.31 (1H, s),
7.58 (2H, d, J=9Hz), 7.93 (2H, d, J=9Hz)

MASS : 424 $(M+H)^+$

Preparation 20

Into a 1 l round bottom flask were added cupric chloride (anhydrous) (7.77 g), acetonitrile (150 ml), lithium chloride (anhydrous) (6.13 g) and n-butyl nitrate (4.47 g) at 20 to 25 ℃ under nitrogen gas. While stirring, {1-(3-chloro-4-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazol-3-yl}amine (10.0 g) was added for 30 minutes at the same temperature. The reaction mixture was stirred for 2 hours and then refluxed for additional 2 hours. After the reaction

was completed, 1N hydrochloric acid (325 ml) and ethyl acetate (150 ml) were added for quenching. The organic layer was separated and washed with brine (180 ml) and then evaporated to give a crude object compound as an oil, which was purified by silica gel column chromatography (SiO_2 50 g, toluene : n-heptane = 3 : 1), and evaporated to give a pure 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazole (7.77 g).

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 3.91 (3H, s), 6.39 (1H, s), 6.80-7.44 (7H, m)

MASS : 365 $(M+H)^+$

Example 1

To a solution of 1-[4-(methylthio)phenyl]-4,4,4-trifluorobutane-1,3-dione (2 g) in acetic acid (30 ml) was added 3-tolylhydrazine hydrochloride (1.27 g). The mixture was refluxed for 2 hours. After cooling, the reaction mixture was poured into ice water and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and filtered. The filtrate was evaporated in vacuo and the resultant oil was dissolved in methanol (100 ml). To this solution was added a solution of Oxone® (potassium peroxy monosulfate) (9.8 g) in water (20 ml) at room temperature. The mixture was stirred for 1 hour and then filtered. The filtrate was partitioned between water and dichloromethane. The organic layer was dried over magnesium sulfate and filtered. The filtrate was evaporated in vacuo and purified by column chromatography on silica gel using dichloromethane as eluent to give 1-(3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (1.98 g).

IR (Nujol) : 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 3.25 (3H, s), 7.06-7.13 (1H, m), 7.32-7.39 (4H, m), 7.56 (2H, d, J=6.7Hz), 7.93 (2H, d, J=6.7Hz)

MASS : 381 $(M+H)^+$

Example 2

A mixture of 1-[4-(methylsulfonyl)phenyl]-4,4,4-trifluorobutane-

1,3-dione (620 mg) and (3-methyl-4-chlorophenyl)hydrazine hydrochloride (425 mg) in acetic acid (2 ml) was refluxed for 1 hour.

After cooling, the solvent was poured into water (50 ml) and stirred for 30 minutes. The resulting precipitates were collected by filtration and washed with water and dried in vacuo. The residue was recrystallized from ethanol to afford 1-(4-chloro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole (569 mg).

mp : 152.0-154.0℃

IR (KBr) : 3128, 3070, 1317, 1286, 1238, 1161, 1128 cm^{-1}

NMR ($CDCl_3$, δ) : 2.39 (3H, s), 3.08 (3H, s), 6.85 (1H, s), 6.92 (1H, dd, J=8.4, 2.7Hz), 7.32 (1H, d, J=8.4Hz), 7.33 (1H, d, J=2.7Hz), 7.43 (2H, d, J=8.6Hz), 7.93 (2H, d, J=8.6Hz)

MASS : 415 $(M+H)^+$

Elemental Analysis for $C_{18}H_{14}ClF_3N_2O_2S$

Calcd. C: 52.12, H: 3.40, N: 6.75

Found C: 51.82, H: 3.30, N: 6.68

Example 3

The following compounds described in (1) to (18) were obtained in a similar manner to that of Example 2.

(1) 1-(4-Fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trifluoromethyl)pyrazole

mp : 134-136℃ (ethanol)

IR (KBr) : 1602, 1315, 1222, 1160, 1157, 1130, 1101 cm^{-1}

NMR (DMSO-d_6, δ) : 2.25 (3H, d, J=1Hz), 3.25 (3H, s), 7.1-7.6 (2H, m), 7.37 (1H, s), 7.4-7.6 (3H, m), 7.9-8.0 (2H, m)

MASS : 399 $(M+H)^+$

(2) 1-(4-Bromo-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

mp : 127.0-129.0℃

IR (KBr) : 3134, 3093, 1315, 1238, 1165, 1128 cm^{-1}

NMR ($CDCl_3$, δ) : 2.41 (3H, s), 3.09 (3H, s), 6.84 (1H, dd, J=8.4, 2.6Hz), 6.85 (1H, s), 7.34 (1H, d, J=2.6Hz), 7.44 (2H, d, J=8.6Hz), 7.51 (1H, d, J=8.4Hz), 7.94 (2H, d, J=8.6Hz)

MASS : 459 $(M+H)^+$ (^{79}Br), 461 $(M+H)^+$ (^{81}Br)

Elemental Analysis for $C_{18}H_{14}BrF_3N_2O_2S$

Calcd. C: 47.07, H: 3.07, N: 6.10

Found C: 47.19, H: 3.05, N: 6.04

(3) 1-(4-Fluoro-3-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trifluoromethyl)pyrazole

mp : 159-160℃ (ethanol)

IR (KBr) : 1612, 1317, 1222, 1162, 1155, 1114 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.76 (3H, s), 6.8-7.0 (1H, m), 7.2-7.4 (2H, m), 7.38 (1H, s), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

MASS : 415 $(M+H)^+$

(4) 1-(4-Chloro-3-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trifluoromethyl)pyrazole

mp : 157-158℃ (ethanol)

IR (KBr) : 1596, 1592, 1315, 1307, 1114, 1106, 1101 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.74 (3H, s), 6.8-7.0 (1H, m), 7.2-7.3 (1H, m), 7.39 (1H, s), 7.4-7.7 (3H, m), 7.9-8.0 (2H, m)

MASS : 431 $(M+H)^+$

(5) 1-(4-Bromo-3-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trlfluoromethyl)pyrazole

mp : 156-157℃ (3:1 n-hexane-ethyl acetate)

IR (KBr) : 1592, 1313, 1162, 1157, 1133 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.75 (3H, s), 6.85 (1H, dd, J=2, 8Hz), 7.20 (1H, d, J=2Hz), 7.39 (1H, s), 7.5-7.7(3H, m), 7.9-8.0 (2H, m)

MASS : 475 $(M+H)^+$

(6) 1-(3-Fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trifluoromethyl)pyrazole

mp : 158.0-160.0℃

IR (KBr) : 3132, 3078, 1315, 1161, 1128 cm^{-1}

NMR ($CDCl_3$, δ) : 2.31 (3H, d, J=1.9Hz), 3.09 (3H, s), 6.84 (1H, s), 6.92 (1H, dd, J=8.1, 2.1Hz), 7.05 (1H, d, J=9.7Hz), 7.19 (1H, t, J=7.7Hz), 7.44 (2H, d, J=8.5Hz), 7.93 (2H, d, J=8.5Hz)

MASS : 399 $(M+H)^+$

Elemental Analysis for $C_{18}H_{14}F_4N_2O_2S$

Calcd. C: 54.27, H: 3.54, N: 7.03

Found C: 54.39, H: 3.48, N: 7.01

(7) 1-(3-Chloro-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trifluoromethyl)pyrazole

mp : 136.5-138.5℃

IR (KBr) : 1315, 1236, 1163 cm^{-1}

NMR ($CDCl_3$, δ) : 2.41 (3H, s), 3.08 (3H, s), 6.84 (1H, s), 6.98 (1H, dd, J=8.3, 2.2Hz), 7.22 (1H, d, J=8.3Hz), 7.42 (1H, s), 7.44 (2H, d, J=8.6Hz), 7.94 (2H, d, J=8.6Hz)

MASS : 415 $(M+H)^+$ (^{35}Cl), 417 $(M+H)^+$ (^{37}Cl)

Elemental Analysis for $C_{18}H_{14}ClF_3N_2O_2S \cdot 1/2H_2O$

Calcd. C: 51.01, H: 3.57, N: 6.61

Found C: 51.15, H: 3.26, N: 6.60

(8) 1-(3-Bromo-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

mp : 159.0-161.0℃

IR (KBr) : 1313, 1234, 1162, 1147 cm^{-1}

NMR ($CDCl_3$, δ) : 2.43 (3H, s), 3.08 (3H, s), 6.84 (1H, s), 7.02 (1H, dd, J=8.2, 2.2Hz), 7.22 (1H, d, J=8.2Hz), 7.44 (2H, d, J=8.6Hz), 7.61 (1H, d, J=2.2Hz), 7.94 (2H, d, J=8.6Hz)

MASS : 459 $(M+H)^+$ (^{79}Br), 461 $(M+H)^+$ (^{81}Br)

Elemental Analysis for $C_{18}H_{14}BrF_3N_2O_2S \cdot 0.3H_2O$

Calcd. C: 46.53, H: 3.17, N: 6.03

Found C: 46.58, H: 2.95, N: 6.01

(9) 1-(3-Fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trifluoromethyl)pyrazole

mp : 178.5-180.5℃

IR (KBr) : 3070, 3016, 1317, 1282, 1238, 1160, 1139, 1097 cm^{-1}

NMR ($CDCl_3$, δ) : 3.09 (3H, s), 3.93 (3H, s), 6.84 (1H, s), 6.88-7.15 (3H, m), 7.43 (2H, d, J=8.6Hz), 7.93 (2H, d, J=8.6Hz)

MASS : 415 $(M+H)^+$

Elemental Analysis for $C_{18}H_{14}F_4N_2O_3S$

Calcd. C: 52.17, H: 3.41, N: 6.76

Found C: 52.23, H: 3.42, N: 6.70

(10) 1-(3-Chloro-4-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]-3-(trifluoromethyl)pyrazole

mp : 184.0-186.0℃

IR (KBr) : 3016, 1315, 1280, 1228, 1159, 1137 cm^{-1}

NMR ($CDCl_3$, δ) : 3.08 (3H, s), 3.94 (3H, s), 6.84 (1H, s), 6.88 (1H, d, J=8.6Hz), 7.06 (1H, dd, J=8.6, 2.6Hz), 7.44 (2H, d, J=8.6Hz), 7.45 (1H, s), 7.93 (2H, d, J=8.6Hz)

MASS : 431 $(M+H)^+$ (^{35}Cl), 433 $(M+H)^+$ (^{37}Cl)

Elemental Analysis for $C_{18}H_{14}ClF_3N_2O_3S \cdot 1/2H_2O$

Calcd. C: 49.15, H: 3.44, N: 6.37

Found C: 49.03, H: 3.18, N: 6.27

(11) 3-(Difluoromethyl)-1-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 154-155℃ (ethanol)

IR (KBr) : 1504, 1315, 1155 cm^{-1}

NMR (DMSO-d_6, δ) : 2.24 (3H, d, J=1Hz), 3.24 (3H, s), 7.12 (1H, s), 7.14 (1H, t, J=54Hz), 7.0-7.3 (2H, m),

7.4-7.5 (1H, m), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

MASS : 381 $(M+H)^+$

(12) 1-(4-Chloro-3-methylphenyl)-3-(difluoromethyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 145-146℃ (ethanol)

IR (KBr) : 1600, 1315, 1153 cm^{-1}

NMR (DMSO-d_6, δ) : 2.34 (3H, s), 3.25 (3H, s), 7.08 (1H, dd, J=2, 8Hz), 7.11 (1H, s), 7.13 (1H, t, J=54Hz), 7.44 (1H, d, J=8Hz), 7.50 (1H, d, J=2Hz), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

MASS : 397 $(M+H)^+$

(13) 1-(4-Bromo-3-methylphenyl)-3-(difluoromethyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 141-142℃ (ethanol)

IR (KBr) : 1598, 1307, 1147 cm^{-1}

NMR (DMSO-d_6, δ) : 2.35 (3H, s), 3.25 (3H, s), 6.99 (1H, dd, J=2, 8Hz), 7.13 (1H, s), 7.15 (1H, t, J=54Hz), 7.50 (1H, d, J=8Hz), 7.5-7.6 (2H, m), 7.64 (1H, d, J=2Hz), 7.9-8.0 (2H, m)

MASS : 441 $(M+H)^+$

(14) 3-(Difluoromethyl)-1-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 161-162℃ (ethanol)

IR (KBr) : 1625, 1594, 1313, 1157 cm^{-1}

NMR (DMSO-d_6, δ) : 2.26 (3H, d, J=1Hz), 3.25 (3H, s), 7.03 (1H, dd, J=2, 8Hz), 7.12 (1H, s), 7.15 (1H, t, J=54Hz), 7.2-7.5 (2H, m), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

MASS : 381 $(M+H)^+$

(15) 1-(3-Chloro-4-methylphenyl)-3-(difluoromethyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 137-139℃ (ethanol)

IR (KBr) : 1602, 1313, 1151 cm^{-1}

NMR (DMSO-d_6, δ) : 2.36 (3H, s), 3.25 (3H, s), 7.1-7.2 (1H, m), 7.12 (1H, s), 7.15 (1H, t, J=54Hz), 7.42 (1H, d, J=8Hz), 7.53 (1H, d, J=2Hz), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

MASS : 397 $(M+H)^+$

(16) 1-(3-Bromo-4-methylphenyl)-3-(difluoromethyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 136-138℃ (ethanol)

IR (KBr) : 1602, 1309, 1147 cm^{-1}

NMR (DMSO-d_6, δ) : 2.37 (3H, s), 3.25 (3H, s), 7.12 (1H, s), 7.15 (1H, t, J=54Hz), 7.18 (1H, dd, J=2, 8Hz), 7.41 (1H, d, J=8Hz), 7.5-7.6 (2H, m), 7.68 (1H, d, J=2Hz), 7.9-8.0 (2H, m)

MASS : 441 $(M+H)^+$

(17) 3-(Difluoromethyl)-1-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 185-186℃ (ethanol)

IR (KBr) : 1596, 1313, 1153 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.87 (3H, s), 7.11 (1H, s), 7.13 (1H, t, J=54Hz), 7.1-7.3 (2H, m), 7.3-7.5 (1H, m), 7.5-7.6 (2H, m), 7.9-8.0 (2H, m)

MASS : 397 $(M+H)^+$

(18) 1-(4-Isopropylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

crystals

mp : 144-146℃

IR (KBr) : 1602, 1506, 1469 cm^{-1}

NMR (DMSO-d_6, δ) : 1.21 (6H, d, J=7Hz), 2.96 (1H, m), 3.26 (3H, s), 7.35 (1H, s), 7.30-7.38 (4H, m), 7.56 (2H, d, J=9Hz), 7.93 (2H, d, J=9Hz)

MASS : 409 $(M+H)^+$

Example 4

To a solution of 1-(3-amino-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole hydrochloride (0.80 g) in ca. 24% hydrobromic acid (16 ml) was added a solution of sodium nitrite (0.14 g) in water (1 ml) while the internal temperature of the reaction mixture was maintained below 0℃. The above mixture was added to an ice-cooled solution of copper(I) bromide (0.30 g) in ca. 24% hydrobromic acid (8 ml) and the mixture was stirred at ambient temperature for 1.5 hours. The reaction mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (elution with chloroform) to give the product, which was recrystallized from diisopropyl ether (3 ml)-ethyl acetate (3 ml) to give 1-(3-bromo-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)-pyrazole (0.39 g).

mp : 164-166℃ (1:1 diisopropyl ether-ethyl acetate)

IR (KBr) : 1600, 1315, 1164, 1157, 1137 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.89 (3H, s), 7.17 (1H, d, J=8Hz), 7.3-7.4 (1H, m), 7.35 (1H, s), 7.5-7.7 (2H, m), 7.75 (1H, d, J=2Hz), 7.9-8.0 (2H, m)

MASS : 475 $(M+H)^+$

Example 5

To a solution of 1-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)-5-[4-(methylthio)phenyl]pyrazole (2.0 g) in dichloromethane (50 ml) was added portionwise m-chloroperbenzoic acid (2.3 g, 80% purity) at 5℃ with stirring. After being stirred at room temperature for 2 hours, the reaction mixture was treated with aqueous solution of sodium thiosulfate and then partitioned between dichloromethane and water. The organic layer was separated, washed with aqueous sodium hydrogen carbonate solution and dried over magnesium sulfate. After evaporation of the solvent, the crude solid was recrystallized from ethanol to give 1-(3-chloro-4-methoxyphenyl)-3-(difluoromethyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (1.8 g).

mp : 169-171℃

IR (Nujol) : 1600, 1510, 1440, 1410, 1350, 1310, 1275, 1150 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.89 (3H, s), 6.87-7.41 (4H, m), 7.56 (1H, s), 7.57 (1H, d, J=8.2Hz), 7.94 (2H, d, J=8.5Hz)

MASS : 413 $(M+H)^+$

Example 6

A mixture of sodium methoxide (169 mg) and ethyl 1-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carboxylate (420 mg) in formamide (5 ml) was warmed at 110℃ for 30 minutes. The reaction mixture was poured into ice-water (50 ml) and the precipitate was collected by filtration, and washed with water and dried in vacuo. To an ice-cooled solution of $POCl_3$ (0.23 ml) in dimethylformamide (3 ml) was added the residue by small portions under nitrogen atmosphere. After 2 hours, the mixture was poured into water (50 ml) and stirred for 30 minutes. The resulting precipitates were collected by filtration and washed with water and dried in vacuo. The resulting residue was purified by column chromatography on silica gel using chloroform and was recrystallized from ethanol to afford 1-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole-3-carbonitrile (297 mg).

mp : 143.5-144.5℃

IR (KBr) : 3118, 2242, 1311, 1232, 1189, 1155 cm^{-1}

NMR ($CDCl_3$, δ) : 2.29 (3H, d, J=2.0Hz), 3.08 (3H, s) 6.91-7.26 (4H, m), 7.13 (1H, s), 7.39 (2H, d, J=8.5Hz), 7.93 (2H, d, J=8.5Hz)

MASS : 356 $(M+H)^+$

Elemental Analysis for $C_{18}H_{14}FN_3O_2S$

Calcd. C: 60.83, H: 3.97, N: 11.82

Found C: 60.57, H: 3.96, N: 11.73

Example 7

The following compounds described in (1) to (10) were obtained according to a similar manner to that of Example 6.

(1) 1-(4-Chloro-3-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 163.0-164.0℃

IR (KBr) : 3118, 3010, 1710, 2240, 1313, 1155 cm^{-1}

NMR ($CDCl_3$, δ) : 2.39 (3H, s), 3.09 (3H, s), 6.92 (1H, dd, J=8.4, 2.5Hz), 6.96 (1H, s), 7.30 (1H, d, J=2.5Hz), 7.34 (1H, d, J=8.4Hz), 7.42 (2H, d, J=8.5Hz), 7.95 (2H, d, J=8.5Hz)

MASS : 372 $(M+H)^+$ (^{35}Cl), 374 $(M+H)^+$ (^{37}Cl)

(2) 1-(4-Bromo-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole-3-carbonitrile

mp : 151.5-152.5℃

IR (KBr) : 3120, 3010, 2242, 1313, 1153 cm^{-1}

NMR ($CDCl_3$, δ) : 2.41 (3H, s), 3.09 (3H, s), 6.83 (1H, dd, J=8.4, 2.3 Hz), 6.96 (1H, s), 7.30 (1H, d, J=2.3Hz), 7.42 (2H, d, J=8.6Hz), 7.53 (1H, d, J=8.4Hz), 7.95 (2H, d, J=8.6Hz)

MASS : 416 $(M+H)^+$ (^{79}Br), 418 $(M+H)^+$ (^{81}Br)

(3) 1-(4-Fluoro-3-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 169.0-171.0℃

IR (KBr) : 3126, 3085, 2242, 1309, 1268, 1249, 1149 cm^{-1}

NMR ($CDCl_3$, δ) : 3.08 (3H, d, J=1.9Hz), 3.85 (3H, s), 6.65 (1H, m), 6.97-7.06 (3H, m), 7.43 (2H, d, J=8.5Hz), 7.92 (2H, d, J=8.5Hz)

MASS : 372 $(M+H)^+$

(4) 1-(4-Chloro-3-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 203.0-205.0℃

IR (KBr) : 3120, 2252, 1309, 1238, 1147 cm^{-1}

NMR ($CDCl_3$, δ) : 3.09 (3H, s), 3.85 (3H, s), 6.64 (1H, dd, J=8.4, 2.4Hz), 6.97 (1H, s), 7.00 (1H, d, J=2.4Hz), 7.33 (1H, d, J=8.4Hz), 7.44 (2H, d,

J=8.5Hz), 7.96 (2H, d, J=8.5Hz)

MASS : 388 $(M+H)^+$ (^{35}Cl), 390 $(M+H)^+$ (^{37}Cl)

(5) 1-(4-Bromo-3-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 212.5-214.5℃

IR (KBr) : 3118, 2252, 1307, 1236, 1149 cm^{-1}

NMR ($CDCl_3$, δ) : 3.09 (3H, s), 3.85 (3H, s), 6.56 (1H, dd, J=8.4, 2.3Hz), 6.96 (1H, d, J=2.3Hz), 7.44 (2H, d, J=8.3Hz), 7.51 (1H, d, J=8.4Hz), 7.96 (2H, d, J=8.3Hz)

MASS : 432 $(M+H)^+$ (^{79}Br), 434 $(M+H)^+$ (^{81}Br)

(6) 1-(3-Fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 167.0-168.0℃

IR (KBr) : 3129, 3072, 2250, 1363, 1149 cm^{-1}

NMR ($CDCl_3$, δ) : 2.32 (3H, d, J=1.9Hz), 3.09 (3H, s), 6.90 (1H, dd, J=8.1, 2.1Hz), 6.95 (1H, s), 7.03 (1H, dd, J=9.5, 2.1Hz), 7.19 (1H, t, J=8.1Hz), 7.42 (2H, d, J=8.6Hz), 7.95 (2H, d, J=8.6Hz)

MASS : 356 $(M+H)^+$

Elemental Analysis for $C_{18}H_{14}FN_3O_2S \cdot 1/2H_2O$

Calcd. C: 59.33, H: 4.15, N: 11.53

Found C: 59.53, H: 3.88, N: 11.50

(7) 1-(3-Chloro-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 174.5-175.5℃

IR (KBr) : 3120, 3012, 2244, 1317, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 2.42 (3H, s), 3.08 (3H, s), 6.95-7.00 (2H, m), 7.24 (1H, d, J=8.4Hz), 7.40 (1H, s), 7.42 (2H, d, J=8.3Hz), 7.95 (2H, d, J=8.3Hz)

MASS : 372 $(M+H)^+$ (^{35}Cl), 374 $(M+H)^+$ (^{37}Cl)

Elemental Analysis for $C_{18}H_{14}ClN_3O_2S$

Calcd. C: 58.14, H: 3.79, N: 11.30

Found C: 57.88, H: 3.74, N: 11.14

(8) 1-(3-Bromo-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole-3-carbonitrile

mp : 179.0-180.0℃

IR (KBr) : 3120, 3010, 2246, 1317, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 2.44 (3H, s), 3.08 (3H, s), 6.96 (1H, s), 7.01 (1H, dd, J=8.1, 2.1Hz), 7.24 (1H, d, J=8.1Hz), 7.42 (2H, d, J=8.6Hz), 7.58 (1H, d, J=2.1Hz), 7.95 (2H, d, J=8.6Hz)

MASS : 416 $(M+H)^+$ (^{79}Br), 418 $(M+H)^+$ (^{81}Br)

(9) 1-(3-Fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 192.0-193.0℃

IR (KBr) : 3068, 3016, 2252, 1315, 1278, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 3.09 (3H, s), 3.94 (3H, s), 6.94-6.96 (3H, m), 7.12 (1H, dd, J=10.1, 2.1Hz), 7.42 (2H, d, J=8.5Hz), 7.94 (2H, d, J=8.5Hz)

MASS : 372 $(M+H)^+$

(10) 1-(3-Chloro-4-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 201.0-203℃

IR (KBr) : 3016, 2250, 1311, 1274, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 3.08 (3H, s), 3.95 (3H, s), 6.89 (1H, d, J=8.8Hz), 6.95 (1H, s), 7.05 (1H, dd, J=8.8, 2.6Hz), 7.42 (2H, d, J=8.6Hz), 7.43 (1H, d, J=2.6Hz), 7.95 (2H, d, J=8.6Hz)

MASS : 388 $(M+H)^+$ (^{35}Cl), 390 $(M+H)^+$ (^{37}Cl)

Example 8

The following compound was obtained according to a similar manner to that of Example 4.

1-(3-Bromo-4-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

mp : 184.0-186.0℃

IR (KBr) : 3064, 3016, 2240, 1309, 1274, 1151 cm^{-1}

NMR ($CDCl_3$, δ) : 3.08 (3H, s), 3.94 (3H, s), 6.86 (1H, d, J=8.8Hz), 6.95 (1H, s), 7.09 (1H, dd, J=8.8, 2.6Hz), 7.42 (2H, d, J=8.4Hz), 7.60 (1H, d, J=2.6Hz), 7.95 (2H, d, J=8.4Hz)

MASS : 432 $(M+H)^+$ (^{79}Br), 434 $(M+H)^+$ (^{81}Br)

Elemental Analysis for $C_{18}H_{14}BrN_3O_3S$

Calcd. C: 50.01, H: 3.26, N: 9.72

Found C: 49.75, H: 3.15, N: 9.59

Example 9

To a solution of {1-(3-methoxyphenyl)-5-[4-(methylthio)phenyl]-pyrazole-3-yl}amine (5 g) in acetic acid (40 ml) and hydrochloric acid (10 ml) was added sodium nitrite (1.7 g) in water (3 ml) at 0℃. This mixture was stirred at 0 ℃ for 1 hour. The diazonium salt prepared above was added to a solution of copper(I) chloride (7 g) in hydrochloric acid (10 ml) at 0℃, and then allowed to warm to ambient temperature. After 1 hour, the reaction mixture was poured into ice water, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate, and filtered. The filtrate was evaporated in vacuo and purified by column chromatography on silica gel eluting with a mixed solution of dichloromethane and n-hexane (1:1). The desired product was dissolved in methanol (100 ml). A solution of Oxone® (potassium peroxy monosulfate) (20 g) in water was added at room temperature and the resultant mixture was stirred for 1 hour and then filtered. The filtrate was extracted with dichloromethane, and washed with water twice. The organic layer was dried over magnesium sulfate, and filtered. The filtrate was evaporated in vacuo to give 3-chloro-1-(3-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (1.32 g).

mp : 103-104℃

IR (Nujol) : 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.24 (3H, s), 3.71 (3H, s), 6.71-6.82 (1H, m), 6.93-7.03 (3H, m), 7.29-7.37 (1H, m), 7.53 (2H, d, J=8.5Hz), 7.92 (2H, d, J=8.5Hz)

MASS : 363 $(M+H)^+$

Example 10

The following compounds described in (1) to (14) were obtained according to a similar manner to that of Example 9.

(1) 3-Chloro-1-(4-fluoro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

IR (KBr) : 1598, 1502 cm^{-1}

NMR ($CDCl_3$, δ) : 2.26 and 2.27 (total 3H, each s), 3.07 (3H, s), 6.52 (1H, s), 6.92 (1H, t, J=3.3Hz), 6.96 (1H, t, J=8.6Hz), 7.21-7.26 (1H, m), 7.40 (2H, dt, J=8.5, 1.9Hz), 7.90 (2H, dt, J=8.5, 1.8Hz).

MASS : 365 (M^+)

(2) 3-Chloro-1-(4-chloro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 180-181℃

IR (Nujol) : 1625, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 3.25 (3H, s), 6.98 (1H, s), 7.05 (1H, dd, J=8.4, 2.5Hz), 7.44-7.49 (2H, m), 7.53 (2H, d, J=8.5Hz), 7.93 (2H, d, J=8.5Hz)

MASS : 382 $(M+H)^+$

(3) 1-(4-Bromo-3-methylphenyl)-3-chloro-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 146-148℃

IR (Nujol) : 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.35 (3H, s), 3.25 (3H, s), 6.93-6.99 (1H, m), 6.99 (1H, s), 7.48 (1H, d, J=2.4Hz), 7.54 (2H, d, J=8.4Hz), 7.61 (1H, d, J=8.5Hz), 7.94 (1H, d, J=8.4Hz)

MASS : 426 $(M+H)^+$

(4) 3-Chloro-1-(4-chloro-3-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 165-166℃

IR (Nujol) : 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.76 (3H, s), 6.81 (1H, dd, J=8.4, 2.3Hz), 7.00 (1H, s), 7.18 (1H, d, J=2.3Hz), 7.47 (1H, d, J=8.4Hz), 7.56 (2H, d, J=8.5Hz), 7.95 (1H, d, J=8.5Hz)

MASS : 398 $(M+H)^+$

(5) 3-Chloro-1-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 160-162 ℃

IR (KBr) : 1614, 1590, 1509 cm^{-1}

NMR (DMSO-d_6, δ) : 2.25 and 2.26 (total 3H, each s), 3.25 (3H, s), 6.97 (1H, s), 7.00 (1H, dd, J=8.8, 1.9Hz), 7.25 (1H, dd, J=10.3, 2.0Hz), 7.34 (1H, t, J=8.3Hz), 7.53 (2H, d, J=8.4Hz), 7.93 (2H, d, J=8.4Hz)

MASS : 365 $(M+H)^+$

(6) 3-Chloro-1-(3-chloro-4-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 159-161℃

IR (Nujol) : 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 2.35 (3H, s), 3.25 (3H, s), 6.98 (1H, s), 7.11 (1H, dd, J=8.2, 2.2Hz), 7.39 (1H, d, J=8.3Hz), 7.51 (1H, d, J=2.2Hz), 7.54 (2H, d, J=8.4Hz), 7.94 (2H, d, J=8.4Hz)

MASS : 382 $(M+H)^+$

(7) 1-(3-Bromo-4-methylphenyl)-3-chloro-5-[4-(methylsulfonyl)phenyl]pyrazole

IR (Nujol) : 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.37 (3H, s), 3.25 (3H, s), 7.14 (1H, dd, J=8.1, 2.2Hz), 6.69 (1H, s), 7.39 (1H, d, J=8.3Hz), 7.54 (2H, d, J=8.5Hz), 7.65 (1H, d, J=2.2Hz), 7.94 (2H, d, J=8.5Hz)

MASS : 426 $(M+H)^+$

(8) 3-Chloro-1-(3-chloro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

mp : 179-180℃

IR (Nujol) : 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 3.25 (3H, s), 3.89 (3H, s), 6.97 (1H, s), 7.17 (1H, d, J=8.8Hz), 7.23 (1H, d, J=8.8Hz), 7.53 (2H, d J=8.6Hz), 7.55 (1H, s), 7.93 (2H, d, J=8.5Hz)

MASS : 398 $(M+H)^+$

(9) 3-Chloro-1-(4-ethylphenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole

crystals

mp : 167-169℃

IR (Nujol) : 1510 cm^{-1}

NMR (DMSO-d_6, δ) : 1.19 (3H, t, J=8Hz), 2.65 (2H, q, J=8Hz), 3.25 (3H, s), 6.95 (1H, s), 7.22 (2H, d, J=9Hz), 7.29 (2H, d, J=9Hz), 7.50 (2H, d, J=9Hz), 7.92 (2H, d, J=9Hz)

MASS : 361 $(M+H)^+$

(10) 3-Chloro-1-(3-chloro-4-ethylphenyl)-5-[4-(methylsulfonyl)-pheny]pyrazole

crystals

mp : 125-127℃

IR (KBr) : 1598, 1490 cm^{-1}

NMR (DMSO-d_6, δ) : 1.18 (3H, t, J=7Hz), 2.72 (2H, q, J=7Hz), 3.25 (3H, s), 6.98 (1H, d, J=2Hz), 7.13 (1H, dd, J=8, 2Hz), 7.39 (1H, dd, J=8, 2Hz), 7.50 (1H, d, J=2Hz), 7.55 (2H, d, J=8Hz), 7.91 (2H, d, J=8Hz)

MASS : 395 $(M+H)^+$ (^{35}Cl), 397 $(M+H)^+$ (^{37}Cl)

(11) 3-Chloro-5-[4-(methylsulfonyl)phenyl]-1-(4-n-propylphenyl)-pyrazole

crystals

mp : 143-144℃

IR (KBr) : 1513 cm^{-1}

NMR (DMSO-d_6, δ) : 0.89 (3H, t, J=7Hz), 1.54-1.65 (2H, m),

2.59 (2H, t, J=7Hz), 3.25 (3H, s), 6.96 (1H, s),
7.19-7.30 (4H, m), 7.50 (2H, d, J=9Hz), 7.90 (2H, d, J=9Hz)
MASS : 375 $(M+H)^+$

(12) 3-Chloro-1-(3-chloro-4-n-propylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole
crystals
mp : 119-122℃
IR (KBr) : 1602, 1490 cm^{-1}
NMR (DMSO-d_6, δ) : 0.92 (3H, t, J=7Hz), 1.57 (2H, dt, J=7Hz),
2.69 (2H, t, J=7Hz), 3.25 (3H, s), 6.99 (1H, s),
7.13 (1H, dd, J=8, 2Hz), 7.38 (1H, d, J=8Hz),
7.51 (1H, d, J=2Hz), 7.54 (2H, d, J=8Hz),
7.94 (2H, d, J=8Hz)
MASS : 409 $(M+H)^+$

(13) 1-(3-Chloro-4-isopropylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifloromethyl)pyrazole
crystals
mp : 84-86℃
IR (KBr) : 1602, 1490, 1469 cm^{-1}
NMR (DMSO-d_6, δ) : 1.21 (6H, d, J=7Hz), 3.30 (1H, m),
3.27 (3H, s), 7.27-7.63 (6H, m), 7.69 (2H, d, J=9Hz)
MASS : 443 $(M+H)^+$

(14) 3-Chloro-1-(4-isopropylphenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole
crystals
mp : 146-148℃
IR (KBr) : 1513 cm^{-1}
NMR (DMSO-d_6, δ) : 1.21 (6H, d, J=7Hz), 2.90-2.97 (1H, m),
3.25 (3H, s), 6.96 (1H, s), 7.10-7.40 (4H, m),
7.51 (2H, d, J=9Hz), 7.9 (2H, d, J=9Hz)
MASS : 375 $(M+H)^+$

Example 11

A solution of sodium nitrite (0.1 g) in water (0.2 ml) was added

a solution of 1-(4-amino-3-methoxyphenyl)-3-chloro-5-[4-(methylsulfonyl)phenyl]pyrazle (0.38 g) in concentrated hydrochloric acid (2 ml) at 0℃ with stirring. The reaction mixture was stirred at 0℃ for 1 hour. 42% Tetrafluoroboric acid (0.5 ml) was added to the solution containing the diazonium salt at 0℃. The resulting mixture was stirred at 0℃ for 2 hours and then left in a refrigerator overnight. The resulting precipitate was collected by filtration, washed with ice water and dried in vacuo, which was heated at 180-200℃ for 10 minutes. Ice water was added and the resulting mixture was extracted with a mixture of tetrahydrofuran and ethyl acetate (1:1). The extract was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel using a mixture of isopropyl ether and tetrahydrofuran (5:1) as eluent to give 3-chloro-1-(4-fluoro-3-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole (55mg).

mp : 140-145℃ (decomp.)

IR (Nujol) : 1600, 1510, 1310, 1250, 1150 cm^{-1}

NMR (DMSO-d_6, δ) : 3.89 (3H, s), 4.01 (3H, s), 6.56 (1H, s), 6.95 (1H, d, J=6.0Hz), 7.21-7.32 (2H, m), 7.53 (2H, d, J=8.0Hz), 7.92 (2H, d, J=8.0Hz)

MASS : 365 $(M+H)^+$

Example 12

A solution of m-chloroperbenzoic acid (0.40 g) in dichloromethane (4 ml) was added dropwise to a solution of 3-chloro-1-(3-cyano-4-methoxyphenyl)-5-[4-(methylthio)phenyl]pyrazole (0.23 g) in dichloromethane (5 ml) and stirred at 0℃ for 1 hour. The mixture was washed with an aqueous solution of sodium bicarbonate, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with a mixture of toluene and ethyl acetate (5:1) to give crystals of 3-chloro-1-(3-cyano-4-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole (197 mg).

mp : 191-194℃

IR (Nujol) : 2235, 1604, 1310, 1150 cm^{-1}

NMR ($CDCl_3$, δ) : 3.10 (3H, s), 3.98 (3H, s), 6.54 (1H, s), 6.95 (1H, d, J=9.0Hz), 7.38 (1H, dd, J=9.0, 2.6Hz), 7.40 (2H, d, J=8.6Hz), 7.54 (1H, d, J=2.6Hz), 7.94 (2H, d, J=8.6Hz)

MASS : 388 $(M+H)^+$

Example 13

To a stirred solution of 3-chloro-1-(4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (278 mg) in a mixture of acetic anhydride (5 ml) and acetic acid (5 ml), nitric acid (sp. gr. 1.42) (0.5 ml) was added at 0℃. After 30 minutes, the resulting mixture was poured into water and extracted with ethyl acetate. The extract was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give crystals. The resulting crystals were washed with ethyl acetate to give 3-chloro-1-(4-methoxy-3-nitrophenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole (297 mg).

mp : 178-180℃ (decomp.)

IR (Nujol) : 1620, 1600, 1535 cm^{-1}

NMR ($CDCl_3$, δ) : 3.09 (3H, s), 4.00 (3H, s), 6.55 (1H, s), 7.07 (1H, d, J=9.0Hz), 7.40 (1H, dd, J=9.0, 2.7Hz), 7.44 (2H, d, J=8.5Hz), 7.75 (1H, d, J=2.7Hz), 7.95 (2H, d, J=8.5Hz)

MASS : 408 $(M+H)^+$

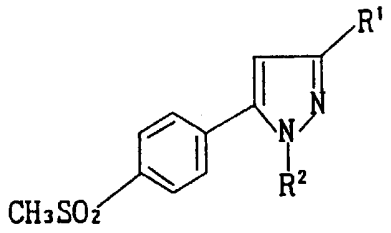
Industrial Applicability

The compound (I) and a salt thereof of the present invention have selective inhibitory activity of COX-II and are useful for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, thrombosis, cancer or neurodegenerative diseases and the like.

This application is based on application No. PO9414 filed in Australia, the content of which is incorporated hereinto by reference.

CLAIMS

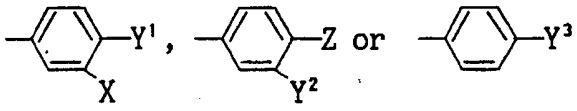
1. A compound of the formula (I) :



(I)

wherein R^1 is chlorine, difluoromethyl, trifluoromethyl or cyano, and

R^2 is a group having the following formula



wherein X is halogen, cyano, nitro or amino,

Y^1 is lower alkyl or lower alkoxy,

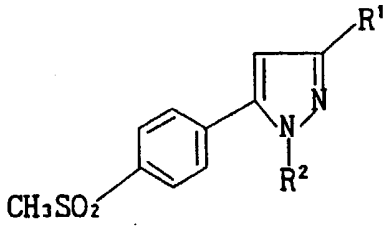
Y^2 is lower alkyl or lower alkoxy,

Y^3 is ethyl, n-propyl or isopropyl, and

Z is hydrogen or halogen,

or a pharmaceutically acceptable salt thereof.

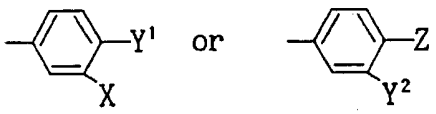
2. A compound of the formula (I) :



(I)

wherein R^1 is chlorine, difluoromethyl, trifluoromethyl or cyano, and

R^2 is a group having the formula



wherein X is halogen, cyano or nitro,

Y^1 is lower alkyl or lower alkoxy,

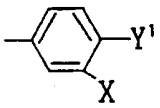
Y^2 is lower alkyl or lower alkoxy, and

Z is hydrogen or halogen.

3. The compound according to claim 1, wherein

R^1 is chlorine and

R^2 is a group having the formula

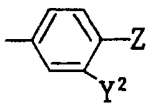


wherein X is halogen or cyano, and Y^1 is lower alkoxy.

4. The compound according to claim 1, wherein

R^1 is trifluoromethyl, and

R^2 is a group having the formula

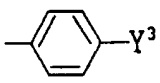


wherein Y^2 is lower alkyl, and Z is hydrogen.

5. The compound according to claim 1, wherein

R^1 is chlorine or trifluoromethyl, and

R^2 is a group having the formula



wherein Y^3 is ethyl, n-propyl or isopropyl.

6. The compound according to claim 1, which is a compound selected

from the group consisting of

(1) 1-(3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole,

(2) 3-chloro-1-(3-cyano-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole,

(3) 3-chloro-1-(3-chloro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole,

(4) 3-chloro-1-(3-chloro-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole

(5) 3-chloro-1-(3-fluoro-4-methylphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole

(6) 1-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]-3-(trifluoromethyl)pyrazole

(7) 3-(difluoromethyl)-1-(3-fluoro-4-methoxyphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole

(8) 3-chloro-1-(4-chloro-3-methylphenyl)-5-[4-(methylsulfonyl)phenyl]pyrazole, and

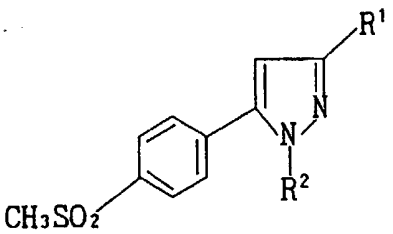
(9) 1-(4-chloro-3-methoxyphenyl)-5-[4-(methylsulfonyl)-phenyl]pyrazole-3-carbonitrile

7. The compound according to claim 1, which is a compound selected from the group consisting of

(10) 3-chloro-1-(4-isopropylphenyl)-5-[4-(methylsulfonyl)phenyl]-pyrazole and

(11) 3-chloro-1-(3-chloro-4-ethylphenyl)-5-[4-(methylsulfonyl)-pheny]pyrazole

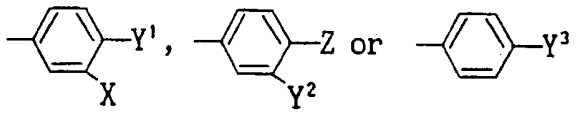
8. A process for preparing a compound of the formula (I) :



(I)

wherein R^1 is chlorine, difluoromethyl, trifluoromethyl or cyano,

R^2 is a group having the following formula



wherein X is halogen, cyano, nitro or amino,

Y^1 is lower alkyl or lower alkoxy,

Y^2 is lower alkyl or lower alkoxy,

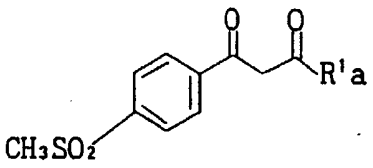
Y^3 is ethyl, n-propyl or isopropyl, and

Z is hydrogen or halogen, or

a pharmaceutically acceptable salt,

which comprises,

(1) reacting a compound of the formula (II-1) :



(II-1)

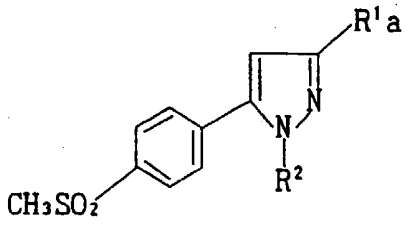
wherein R'a is difluoromethyl or trifluoromethyl,

or its salt, with a compound of the formula (III) :

$$R^2\text{-}NH\text{-}NH_2 \qquad \text{(III)}$$

wherein R^2 is as defined above

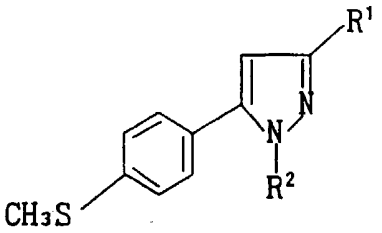
or its salt, to give a compound of the formula (I-1) :



(I-1)

wherein R'a and R^2 are as defined above,

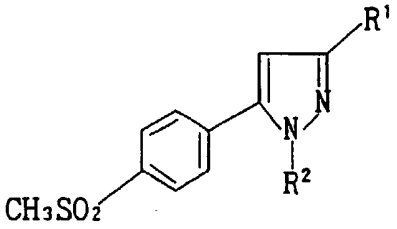
(2) oxidizing a compound of the formula (IV) :



(IV)

wherein R^1 and R^2 are as defined above

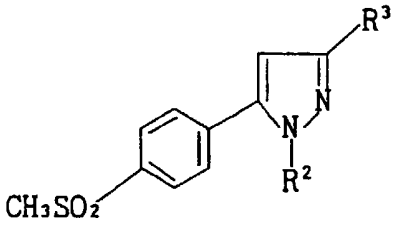
to give a compound of the formula (I) :



(I)

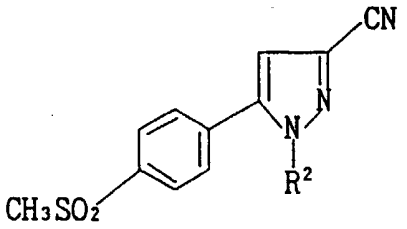
wherein R^1 and R^2 are as defined above

(3) subjecting a compound of the formula (V) :



(V)

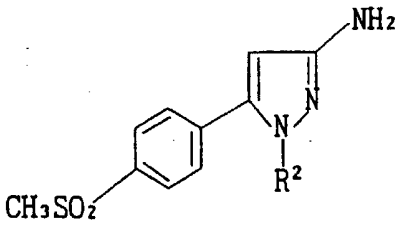
wherein R^3 is carboxy or esterified carboxy and R^2 is as defined above, or its salt, to amidation and then dehydration, to give a compound of the formula (I-2) :



(I-2)

wherein R^2 is as defined above, or

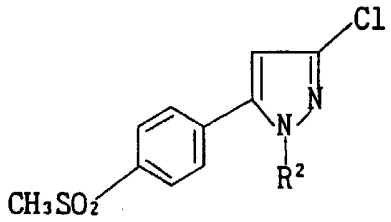
(4) subjecting a compound of the formula (VI) :



(VI)

wherein R^2 is as defined above,

or its salt, to chlorination to give a compound of the formula (I-3) :



(I-3)

wherein R^2 is as defined above.

9. A pharmaceutical composition comprising the compound of claim 1, as an active ingredient, in association with a pharmaceutically non-toxic carrier or excipient.
10. A compound of claim 1 for use as a medicament.
11. A COX-II inhibiting agent comprising the compound of claim 1.
12. A method for the treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegenerative diseases which comprises administering an effective amount of the compound of claim 1 to human beings or animals.
13. Use of the compound of claim 1 for the manufacture of a medicament for treatment and/or prevention of inflammatory conditions, various pains, collagen diseases, autoimmune diseases, various immunity diseases, analgesic, thrombosis, cancer or neurodegenerative diseases in human beings or animals.

INTERNATIONAL SEARCH REPORT

In ational Application No
PCT/JP 98/04150

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D231/16 C07D231/12 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 418 845 A (FUJISAWA PHARMACEUTICAL CO) 27 March 1991 cited in the application see, e.g. ex. 5-1,8,9,10,11,12; 6; 7-2,4; 11-3; 15-6,7,9,10; 17-10,13,16; 26; 34-6; 56 ---	1-11,13
Y	WO 95 15316 A (GRANETS MATTHEW J ;MIYASHIRO JULIE M (US); SEARLE & CO (US); TALLE) 8 June 1995 see, e.g. ex. 31, 43, 37, 38, 45, 59, 64, 71-73, 78, 82, 121, 130, 134-136, 138, 262 ---	1-11,13
A	EP 0 554 829 A (FUJISAWA PHARMACEUTICAL CO) 11 August 1993 cited in the application see, e.g. 3, 8(1)-(7), 29-31 --- -/--	1-11,13

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 November 1998	02/12/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Frelon, D

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ıtional Application No
PCT/JP 98/04150

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ³	Citation of document. with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 13755 A (FUJISAWA PHARMACEUTICAL CO. LTD) 17 April 1997 see claim 1	1-11,13

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 98/04150

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 12 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ational Application No
PCT/JP 98/04150

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0418845 A	27-03-1991	AT 126216 T	15-08-1995
		AU 637142 B	20-05-1993
		AU 6307290 A	18-04-1991
		CA 2025599 A	23-03-1991
		CN 1050382 A	03-04-1991
		DE 69021472 D	14-09-1995
		DE 69021472 T	25-01-1996
		DK 418845 T	18-09-1995
		ES 2088933 T	01-10-1996
		GR 3017100 T	30-11-1995
		HU 9500344 A	28-09-1995
		IE 68857 B	24-07-1996
		IL 95675 A	31-03-1996
		JP 2586713 B	05-03-1997
		JP 3141261 A	17-06-1991
		NO 301006 B	01-09-1997
		PT 95389 A,B	22-05-1991
		RU 2021990 C	30-10-1994
		RU 2059622 C	10-05-1996
		US 5134142 A	28-07-1992
WO 9515316 A	08-06-1995	US 5466823 A	14-11-1995
		US 5521207 A	28-05-1996
		AU 690609 B	30-04-1998
		AU 1171495 A	19-06-1995
		CA 2177576 A	08-06-1995
		CN 1141630 A	29-01-1997
		CZ 9601503 A	11-12-1996
		EP 0731795 A	18-09-1996
		FI 962249 A	29-05-1996
		HU 74180 A	28-11-1996
		JP 9506350 T	24-06-1997
		NO 962184 A	29-05-1996
		PL 314695 A	16-09-1996
		US 5510496 A	23-04-1996
		US 5563165 A	08-10-1996
		US 5508426 A	16-04-1996
		US 5516907 A	14-05-1996
		US 5504215 A	02-04-1996
		US 5753688 A	19-05-1998
		US 5760068 A	02-06-1998
		ZA 9409418 A	28-11-1995
EP 0554829 A	11-08-1993	AU 663149 B	28-09-1995
		AU 3217493 A	12-08-1993
		CA 2088835 A	06-08-1993
		CN 1075959 A	08-09-1993
		HU 9500347 A	28-09-1995
		IL 104311 A	13-07-1997
		JP 5246997 A	24-09-1993
		MX 9300579 A	30-09-1993
		US 5550147 A	27-08-1996
		US 5670533 A	23-09-1997
		ZA 9300077 A	04-08-1993
WO 9713755 A	17-04-1997	AU 7146196 A	30-04-1997
		CA 2234511 A	17-04-1997
		EP 0856000 A	05-08-1998